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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

JAN 13 2003

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P. O. Box 390
Shawnee Mission, KS 66201

Subject: CRP Testing for New Advantage Products

Advantage Plus 9	11556-REA
Advantage Plus 10	11556-REI
Advantage Plus 20	11556-REL
Advantage Plus 18	11556-REO
Advantage Plus 55	11556-RET
Advangage Plus 100	11556-RGN

Your Submission date, November 13, 2002

Dear Mr. McNamara:

The Agency has received and reviewed your Child Resistant Packaging (CRP) study protocol for all six of the above listed products. After careful review, there are a number of questions/clarifications concerning the testing protocols. A copy of the results are attached. Please review the results and resubmit in accordance with the directions given by Dr. Gross. If I can be of assistance in anyway, call me at 703 305-5409.

Sincerely,

/s/

Dani Daniel
Insecticide/Rodenticide Branch
Registration Division 7505C

Attachment:

CHILD-RESISTANT PACKAGING REVIEW
Technical Review Branch

IN 12/03/02 OUT 12/11/02

Reviewed by Rosalind L. Gross 12/11/02

EPA Reg. No. or File Symbol 11556-REA,11556-REI, 11556-REL, 11556-RET, 11556-RGN, 11556-REO

DP Barcode D287000, D287001, D287003, D287004, D287005, D287006

EPA Petition or EUP No. _____

Date Division Received 11/18/02

Type Product(s) Insecticide

Data Accession No(s). _____

Product Mgr./Chemical Review Mgr/Contact Person PM 04 (Helen Daniel)
Division RD

Product Name(s) Advantage Plus 9 for Cats, Advantage Plus 10 for Dogs, Advantage Plus 20 for Dogs, Advantage Plus 55 for Dogs, Advantage Plus 100 for Dogs, Advantage Plus 18 for Cats

Company Name(s) Bayer Corp

Submission Purpose Review protocol testing scheme for child-resistant effectiveness test and senior adult use effectiveness test along with other requirements to fulfill CRP requirements for this product

Active Ingredient(s), PC code, & % Imidacloprid 9.1%

Summary

The child resistant effectiveness and senior adult use effectiveness test protocols submitted for these 6 products resulted in a number of questions/clarifications regarding the product such as what was the actual child-resistant package (CRP), what was the definition of a child failure, etc. The result was a telephone conference call on 12/5/02 with the registrant and the CRP testing organization (see attached questions/clarifications) and a 12/9/02 follow-up telephone call between Rosalind L.

Gross, EPA and Dr. Harish Chopade, Bayer. The conclusion of the aforementioned conversations and the review of the child resistant effectiveness and senior adult use effectiveness test protocols submitted for these 6 products is that **either the blister or the tube itself must be child-resistant. All three size tubes and both package sizes for each tube size must be tested. The exception** is the 1 ml or less tube size requires CRP only if at least 9 tubes are in a retail package. **However, unless** the packaging for the one ml or **less tube sizes is in a different package (not just a different color), but a different design/style than the CRP sizes it will also have to be tested. A bracketing scheme with prior Agency approval is suggested.**

A new submission with a **testing scheme for the three** tube **sizes and the two package sizes should** be **approved prior to testing.** Samples of the package to be used for CRP testing must be provided. For the CRP requirements for this product to be met the data for the child resistant effectiveness and senior adult use effectiveness tests must be submitted both electronically in **accordance with PR 97-9** and a hardcopy, also a CRP certification needs to be submitted.

Some of the problems with the submission are:

1. The chart of the number of tubes representing a failure for child test submitted by the registrant is incorrect. This must be corrected.

2. Testing one tube size (4.0ml) in one package size (6 tubes) is insufficient. Potentially 6 packages need to be subjected to CRP testing. A bracketing scheme with prior Agency approval is suggested.

3. The tube itself or the blister must be the child-resistant package rather than a combination of the two being the child-resistant.

4. Note labeling indicating this is a single use tube must be provided to the Agency.

5. If the **blister** is the package tested for CRP: The children are given the number of blister cards that represent a toxic or harmful amount of product at the beginning of the test (e.g. 1 ml tube size or less 2 blister cards for access to at least 9 tubes). A **blister/package failure is access/potential to the tube**, the tube does not have to be physically removed from the blister or opened. If the tube is the package tested for CRP: The children are given the number of tubes that represent a toxic or harmful amount of product at the beginning of the test (e.g. 1 ml tube size or less access to at least 9 tubes with a maximum of 12 tubes). A **tube/package failure is access/potential to the contents of the tube in whole or in part**, which means even a pinhole size opening in the tube is a failure since the product is a liquid. A **child failure needs to be correctly defined in each test report** based on the tube size and the number of tubes

given to the child to represent a toxic or harmful amount in that test (e.g.1 ml tube size or less access to at least 9 tubes). **The package demonstration of how to open a package by the tester (child test protocol item 25)** and the **definition of a package failure (child test protocol item 30) need to be adjusted dependent on whether the blister or the tube is the CRP.**

6. If the **blister** is the package tested for CRP: The senior test needs to be modified to reflect the need only to remove the tube from the blister. A **package failure needs to be defined.** If the **tube** is the package tested for CRP: The senior test needs to be modified to reflect the need only to remove the product from the tube. A **package failure needs to be defined.**

Analysis of Data and Discussion

Product/Package Information

The registrant indicated the product is to be marketed in 3 tube sizes which are: one tube size for the 0.4, 0.8, and 1 ml, a second tube size for the 2.5 ml, and a third tube size for the 4.0ml. The product is to be marketed for all three tube sizes in a 4 tube package and a 6 tube package. **Testing one tube size (4.0ml) in one package size (6 tubes) is insufficient.** Potentially 6 packages need to be subjected to CRP testing. A bracketing scheme with prior Agency approval is suggested.

Based on toxicity the tube size for 1 ml or less requires CRP only if at least 9 tubes are in a retail package. However, **unless** the packaging for the **one ml or less tube sizes is in a different package (not just a different color), but a different design/style than the CRP sizes it will also have to be tested.** This requirement is based on the fact that using the same package for all three tube sizes constitutes voluntary use of CRP, which per 40 CFR 157.30 is required to meet the same standards as mandatory CRP.

The package for each of the tube sizes and package sizes consists of a single use tube in a blister package. For the dog products the blister package is then placed in an outer cardboard carton, for the cat products the blister package is placed on a cardboard card. **The tube itself or the blister must be the child-resistant package rather than a combination of the two being the child-resistant.** The rationale for this statement is that the tube is the immediate package and the blister is once removed from the immediate package. **Both** the blister and the outer cardboard carton (in the case of dog products) are considered to be secondary packaging. 40 CFR 157.27 Unit packaging allows for either the unit package (the tube in this instance) or the outer package (the blister in this instance) to be CRP. **Note labeling indicating this is a single use tube must be provided to the Agency.**

Toxicity Data

The registrant indicated an oral LD_{50} of 1283 mg/kg in male rats and t000mg/kg in female rats. Based on a worst case scenario the registrant decided to use the female rat oral LD_{50} of 1000mg/kg. The toxic or harmful amount of product for a 25 lb (11.4kg) child using the oral LD_{50} 1g/kg and product specific gravity of 1.092g/ml is 11.4g = 10.44ml. Based on the toxic or harmful amount of 11.4g or 10.44ml of product the number of tubes used for a failure based on tube size is as follows:

tube size (ml)	# of tubes a failure for child test
0.4	27 (therefore access to 9 tubes is a failure)
0.8	14 (therefore access to 9 tubes is a failure)
1.0	11 (therefore access to 9 tubes is a failure)
2.5	5
4.0	3

The chart of the number of tubes representing a failure for child test submitted by the registrant is incorrect. It must be corrected.

Child Test

If the **blister** is the package tested for CRP: The children are given the number of blister cards that represent a toxic or harmful amount of product at the beginning of the test (e.g. t ml tube size or less 2 blister cards for access to at least 9 tubes). A **blister/package failure is access/potential to the tube**, the tube does not have to be physically removed from the blister or opened. If the **tube** is the package tested for CRP: The children are given the number of tubes that represent a toxic or harmful amount of product at the beginning of the test (e.g. 1 ml tube size or less access to at least 9 tubes with a maximum of 12 tubes). **A tube/package failure is access/potential to the contents of the tube in whole or in part**, which means even a pinhole size opening in the tube is a failure since the product is a liquid. **A child failure needs to be correctly defined in each test report** based on the tube size and the number of tubes given to the child to represent a toxic or harmful amount in that test (e.g.1 ml tube size or less access to at least 9 tubes). The package demonstration of how to open a package by the tester (child test protocol item 25) and the definition of a

package failure (child test protocol item 30) need to be adjusted dependent on whether the blister or the tube is the CRP.

Senior Adult Use Effectiveness Test

If the **blister** is the package **tested** for CRP: The senior **test needs to be** modified to reflect the need only to remove the tube from the blister. A **package failure needs to be defined**. If the **tube** is the package tested for CRP: The senior test needs to be modified to reflect the need only to remove the product from the tube. A **package failure needs to be defined.**

Final Report and Addendum

When these studies are submitted both an electronic (per PR Notice 97-9) and hard copies must be submitted. The hard copy Final Report or an Addendum to it in addition to the requirements in 16 CFR 1700.20 should include:

A sample of the child-resistant blister card with the tube or the package to be tested.

Indicate how many tubes/blister cards the child got at the start of the test.

Report the number of **tubes/blisters each child accessed** not just whether or not it was a child failure.

Define a package failure.

Define a child failure.

Describe the Senior Adult Protocol used.

Define a Senior Adult test failure.

Include a copy of the instructions used in Senior Adult Use Effectiveness test.

Note any change in the color, composition, size,, etc. for the tube/blister from what was originally tested may necessitate retesting.

A CRP certification in accordance with 40 CFR Part 157 must be submitted. Note if any changes occur in the color, composition, size, etc. for the tube/blister from what was originally tested a new CRP certification is required and retesting may be required.

Conclusion

In conclusion, a new submission with a testing scheme for the three tube sizes and the two package sizes should be approved prior to testing. Samples of the package to be used for CRP testing must be provided. For the CRP requirements for this product to be met the data for the child resistant effectiveness and senior adult use effectiveness tests must be submitted both electronically in accordance with PR 97-9 and a hardcopy, also a CRP certification needs to be submitted.

All test samples from the child test panel and senior adult test panel should be retained at a minimum until after EPA has accepted the test data and CRP certification. If a question arises as to whether or not a failure exists EPA may ask for the test sample to be examined and a failure to do so could be problematic.

CRP Testing for Advantage Plus
EPA Reg. No. 11556-REA, 11556-REI, 11556-REL, 11556-RET, 11556-RGN, 11556-REO

There are a number of questions/clarifications that should accompany the CRP testing protocols before testing is undertaken. The child test panel and senior adult test panel are following the general procedures in 16 CFR 1700.20. However there are some details not in 16 CFR 1700.20 that need to be addressed in terms of what packages are tested and what type of information is seen in the written final study report. These questions/clarifications are as follows:

1. Product is to be marketed in tubes with 0.4, 0.8, 1.0, 2.5, and 4.0 ml of product. Will the actual physical size for each of these 5 tubes be different? If not, please indicate which product sizes (e.g. 0.4, 0.8, 1.0 ml) will be in the same physical size tube. This should be in the written final study report or in a cover letter accompanying it. Note each physical size tube will need to be tested and the data reviewed.

2. The product is to be marketed in a nonchild-resistant tube in a child-resistant blister card. Have I understood this correctly?

3. Each child-resistant blister card would contain 6 tubes. Are there any other blister card sizes (e.g. a 4 tube child-resistant blister card) planned for the present or the future? Each blister card size would have to be tested. This means 5 different physical size tubes in two different blister card sizes each would require 10 tests. Should some type of bracketing scheme be considered? Note testing the 4 ml size alone will not suffice. Were you planning to test other sizes?

4. Since the tube is nonchild-resistant, the labeling would have to support single use because once the tube is out of the blister it is no longer CRP.

5. According to the toxicity data presented the 0.4, 0.8, 1.0 ml sizes would define a child failure as access to 9 units of the blister card per 16 CFR 1700.20. If only 6 tubes of product are in child-resistant blister card, then that size is not subject to CRP (a toxic or harmful amount is not available). However, if all 5 sizes of product (0.4, 0.8, 1.0, 2.5, and 4.0 ml) use the same package then, the 0.4, 0.8, 1.0 ml sizes must be in CRP and each child would have to receive 12 tubes/2 blister cards at the beginning of the test so that a child has potential access to a toxic or harmful amount at the beginning of the test.

6. Why is a child being given a second blister card for the 4 ml product size test?

7. According to the toxicity data presented the 0.4, 0.8, 1.0 ml sizes would define a child failure as access to 9 units of the blister card per 16 CFR 1700.20. The definition

of a child failure as access to 9 units of the blister card for these product sizes should be in the written final study report. The definition of a child failure as access to 4 or 2 units of the blister card for the 2.5 and 4ml product sizes should be in the written final study report.

8. Since the tube is nonchild-resistant and the blister card is the child-resistant feature an opening or blister failure would be opening the blister such that the tube is available. The child would not have to do anything to the tube for it to be a failure. Why have you stated it as involving the tube in item 30 page 7? There should be agreement between EPA and Bayer as to what "opening the blister such that the tube is available" means before testing. Digital photos as a jpg file of the definition of a blister failure pretesting would be good.

9. Records should be kept of the number of tubes accessed per child in each 5 minute period and for the full 10 minutes. Will this be done?

10. What does a sample of the child-resistant blister card with the tube look like? Please send a physical sample.

11. Will the test data be formatted in accordance with PR97-9, since it will have to be submitted for review electronically as well as written format?

12. All test samples from the child test panel and senior adult test panel should be retained at a minimum until after EPA has accepted the test data and CRP certification. If a question arises as to whether or not a blister failure exists EPA may ask for the test sample to be examined and a failure to do so could be problematic.

13. For the senior adult test panel will the participant be given a blister, asked to open it, remove one tube, and squirt a small amount into something? If so the opening of the blister and removal of the tube should be specified in the written final study report. A copy of the instructions given to the seniors should be in the written final study report or in a cover letter accompanying it. The company would have to include these instructions in the package labeling approved for marketing.

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JAN 12 2001

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Applications for New Advantage Products
Reg. No. 11556-REA, REO, REI, REL, RET, RGN
Your submission date, April 7, 2000

Dear Mr. McNamara:

The labeling referred to above, submitted in connection with the above registrations under the Federal Insecticide, Fungicide, and Rodenticide Act have been reevaluated based on the additional information given, however, there are a number of things that the Agency insist upon and Bayer must comply but registration will be issued.

Enclosed are the conclusions issued by the Product Chemistry Branch. Please read the review and make changes as specified. Upon making the changes, please resubmit your labels and CSFs. If there are question, call me at 703 305-5409.

Sincerely,

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

Product ingredient source information may be entitled to confidential treatment

DATE: 22/NOV/2000

SUBJECT: **PRODUCT CHEMISTRY REVIEW OF MP [ ] EP's [X]**

DP BARCODE No.: D270181
REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
AND
DP BARCODE No.: D270183
REG./File Symbol No.: 11556-REI ← FILE
PRODUCT NAME: Advantage Plus 10 for Dogs
AND
DP BARCODE No.: D270184
REG./File Symbol No.: 11556-REL
PRODUCT NAME: Advantage Plus 20 for Dogs
AND
DP BARCODE No.: D270182
REG./File Symbol No.: 11556-REO
PRODUCT NAME: Advantage Plus 18 for Cats
AND
DP BARCODE No.: D270186
REG./File Symbol No.: 11556-RET
PRODUCT NAME: Advantage Plus 55 for Dogs
AND
DP BARCODE No.: D270188
REG./File Symbol No.: 11556-RGN
PRODUCT NAME: Advantage Plus 100 for Dogs

COMPANY: Bayer Corporation

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch (TRB)/RD (7505C)
Linda L Kutney 11-22-00

TO: Tina Levine/Dani Daniel, PM #4
Insecticide Branch/RD(7505C)

INTRODUCTION

The Bayer Corporation previously applied for registration of six new Advantage Plus insecticides [redacted] intended to kill fleas on different sizes of cats and dogs. The new products differs from the previous ones in that they include an insect growth regulator, pyriproxyfen, to help control flea eggs, and contains an additional inert. TRB

Product ingredient source information may be entitled to confidential treatment

(L. Kutney) reviewed these data on June 2, 2000. All six products contain identical CSFs (dated 4-7-00) and separate proposed labels (dated 4-7-00). This review summarizes the Agency conclusions included in the June 2, 2000, review, Bayer's October 27, 2000, rebuttal to the Agency's conclusions and the Agency's response to Bayer's rebuttal.

Item 1

Agency Conclusion of June 2, 2000

Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical.

Bayer's Rebuttal of October 27, 2000

"The nominal concentrations of a.i.'s on the CSFs and the draft product labels are identical. For example, the upper and lower certified limits for imidacloprid are 9.6% and 8.6%, respectively, and the nominal concentration for imadacloprid is 9.1% on both the CSF and the draft labeling. Please note, the upper, lower and nominal concentrations for imidacloprid are identical to those on the CSFs and labels for the 7 registered Advantage products (EPA Reg. Nos. 11556-116 through 11556-122). For ease of reference, a CSF for Advantage 10, EPA Reg. No. 11556-117, is enclosed. The Confidential Appendix of the review states *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* As 8.9% is not on the CSF, we surmise that this value may have been calculated to correct for percent purity of the technical material. Thus, the nominal concentrations of the a.i.'s on the CSF are identical to the label concentrations, and the CSF and draft labeling for the Advantage Plus products are correct."

Agency Response of November 21

Subpart D-Product Chemistry Data Requirements, May 24, 2000, draft, defines the nominal concentration required by 158.155 as the "amount of active ingredient that is most likely to be present in the product when produced," in other words, the %active ingredient in the product (See also OPPTS 830.155, p.1). In addition, the nominal concentrations on the CSF and the draft label must be identical.

The Agency reiterates that *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* Bayer is correct in assuming that the nominal concentration of imidacloprid is corrected to account for the fact that technical imidacloprid a.i. [redacted] pure, and technical pyriproxyfen a.i. [redacted] pure. The nominal concentration of each a.i. from the CSF is calculated, as follows:

nominal concentration of the a.i. =

The amount of each a.i. (kg), column 13a / Total weight of components in column 13a x (% purity of a.i. technical)

Bayer may either make sure that the label stated concentration is adjusted to be identical to the nominal concentrations of the a.i.'s or adjust the amount of each a.i. component so that the nominal concentration of each a.i. is identical to the proposed label concentration.

Item 2

Agency Conclusion of June 2, 2000

The name and address of the suppliers of inerts should be included on a revised CSF.

Bayer's Rebuttal of October 27, 2000

"Bayer acknowledges that the supplier(s) for "specialty" or proprietary materials must be listed on the CSF, but for those chemicals which are considered "commodity" chemicals, Bayer has not routinely listed the suppliers. As examples, the CSF's for the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) do not list the suppliers. The enclosed CSF for Advantage 10, EPA Reg. No. 11556-117, is a specific example. The Agency has permitted this in the past and acknowledges this practice which allows a change in source of these commodity chemicals without notification as permitted under PR Notice 98-10, Section III, B, 1.

As all of the inert ingredients in the proposed formulation for the A Plus products are commodity chemicals and are the same commodity chemicals which are in the Advantage formulation (Reg Nos 11556-116 through 11556-122) for which the Agency did not require the suppliers to be listed, Bayer would prefer not to list the suppliers of these chemicals for the Advantage Plus formulation."

Agency Response of November 21

The Agency routinely requests the names and addresses of suppliers of inerts on CSF's in order to be able to contact the supplier about the contents of their inerts, when necessary. The Instructions to EPA Form 8570-4, for Confidential Statement of Formula, Supplier Name and Address, number 11, specify that the Registrant should, "Provide the name and address of the supplier of each component in the (CSF) formulation. If one or more components will be obtained from more than one source, specify the names and addresses of the alternate sources also." There is no exception for "commodity chemicals."

A revised CSF including the name and address of the suppliers of inerts is still required.

Item 3

Agency Conclusion of June 2, 2000

The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled "Confidential Business Information." This is a 3-97 FIFRA requirement (Section 10 (d)(1))needed for enforcement purposes, etc.

Bayer's Rebuttal of October 27, 2000

"One copy of the method without any "confidential" markings is included with this letter. Please note that this method is to be used for all six product applications.

Agency Response of November 21

An analytical method labeled "CBI" is not permitted as an enforcement method. The Agency acknowledges the receipt of the enforcement analytical method without this label and considers that the requirement for analytical method (40CFR 158.180) is now satisfied.

Item 4

Agency Conclusion of June 2, 2000

Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the Product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

Bayer's Rebuttal of October 27, 2000

Explodability "The OPPTS Test GDL 830.6316 for Explodability states 'The explodability test is necessary for use in precautionary labeling of pesticides when the product is potentially explosive.' Previous Agency guidance ('Roadmap for Guidance to Product Chemistry Guidelines' report from Anne Lindsay...) on this data requirement stated the requirement is for dusts and dusts from granular or powdered products. The Advantage Plus formulation is a liquid formulation. Moreover, it is not potentially explosive. The currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive..."

Agency Response of November 21

Explodability

The Agency is aware that Advantage Plus is a liquid formulation. Section 158.190 of the 40 Code of Federal Regulations states that explodability testing is required if the product is

potentially explosive. However, the requirement for data concerning explodability definitely applies to liquid end use products as well as dusts and dusts from granular or powdered products. In fact, some liquids have a very high explosive potential, e.g., nitroglycerine.

Registrants are obliged to characterize the explodability of new end use products, in the absence of data or documentation to the contrary, the Agency may consider that any new product may be potentially explosive. Bayer has now certified that the currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive...due to substitution of substitution of organic some organic solvent with water.

The requirement for explodability testing, OPPTS Test GDL 830.6316, is now satisfied.

Bayer's Rebuttal of October 27, 2000

Storage Stability As stated in 830.1000 Background for Product Properties Test Guidelines for the (viiii) OPPTS 830.6317 Storage Stability discussion on p 17:

- "The requirement for data (storage stability) on the EP applies on when: The product use pattern is one for which performance (efficacy) data are required (40CFR 158.640); the results of the storage stability study indicate that the concentration of any active ingredient is not within the certified limits or degradates of toxicological significance are detected in the study; or product instability is suspected or incidents of instability are reported."

Advantage Plus does not meet any of these conditions, as it is an EP, it is not registered for the use patterns for which efficacy data are required under 40 CFR 158.640, and the product/a. i.'s are known to be stable. Thus, storage stability data for the Advantage Plus formulation should not be required for submission.

Agency Response of November 21

Product Properties Test Guidelines OPPTS 830.6317 (b) for Storage Stability states that, "The objective of storage stability testing is to determine how long the product will retain the percent a.i. in its packaging material corresponding to its useful shelf life. The storage stability study provides data on change (or lack of change) in product composition over time, If certain ingredients decompose, other new chemicals are formed whose toxicity and other characteristics must be considered." Bayer should read 830.6317 for details concerning the requirements for storage stability testing. Storage stability testing is required end-use formulations, including the Advantage Plus formulation.

Bayer's Rebuttal of October 27, 2000

Miscibility GDL 830.6319 for Miscibility states:

- "This test is intended to determine whether a pesticide solution is suitable for application

after dilution with oil or other nonpolar solvents where applicable, instead of water. Data on miscibility also provide necessary information to support acceptable labeling for tank mix and spray applications (if the tank mix of the pesticide product is oil based or diluted with oil)."

Agency Response of November 21

GDL OPPTS 830.6319 for miscibility states, "Data on the physical and chemical characteristics of pesticide products are used to confirm or provide supportive information on their identity. Such data are used in reviewing the production or formulation process to produce the pesticide or product." However, the Agency is willing to concede that, as stated in 40 CFR 158.190 "the miscibility test is required if the liquid is an emulsifiable liquid and is to be diluted with petroleum solvents." Provided there is no alteration of use pattern for Advantage Plus which would involve dilution with petroleum or non-polar solvents, there will be no requirement imposed for miscibility testing.

Bayer's Rebuttal of October 27, 2000

Dielectric Breakdown Voltage

...Advantage Plus is to applied directly to dogs and cats in small volumes...use is not around electric equipment...

Agency Response of November 21

GDL 830.6321 states that dielectric breakdown voltage is required when the pesticide product is used on or in the vicinity of electrical equipment and electrical conduits. Dielectric breakdown voltage will not be required for this product, provided there is no alteration of use pattern which would increase exposure of the pesticide handlers to electrical equipment or electrical conduits.

The requirement for data concerning dielectric breakdown voltage is now satisfied.

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.: D265763 REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY: Bayer Corporation

1 Reviewer: Linda L. Kutney

2. Company: Bayer Corporation

3. Type of Submission: Registration [X] Reregistration [ ] New [X] Resubmission [ ] Amendment [ ] "ME-TOO" [X] Alternate Formulation [ ] Experimental Use Permit [ ] Other (Specify)

4. If "Me-TOO" Registration, this product is [ ] is not [X] similar or substantially similar to EPA's Reg. No.:
11556-116
If not, comment in Confidential Appendix on the significant differences between the registered and the new source.

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
- Non-integrated formulation system.....[X]
- Are all technical grade active ingredients used registered? ● yes [X] ● no [ ], If no, specify
- Integrated formulation system.....[ ]

6. Clearance of intentionally added ingredients in the formulation for the intended use (indicate in the Confidential Appendix those that are not cleared; the PC Codes should be provided by the chemist on the CSF for those that are cleared):

6(a) Formulation intended for food use under 40CFR§180.1001:
● yes [ ] ● no [X] ● Some are cleared, others are not [ ]
Cleared under list: ● c[ ] ● d[ ] ● e [ ]
Are there any limitations for use as an inert under 40CFR§180.1001?

● yes [ ] ● no [X], If yes, specify

6(b) Formulation intended for non-food use:
● yes [X] ● no [ ] ● Some are cleared, others are not [ ]

6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199,e.g.,(a) indirect food additives, such as food contact surface sanitizers; adhesives, coatings, paper and paperboard products that may contact food in packaging or holding; & (b) substances

Product ingredient source information may be entitled to confidential treatment

generally recognized as safe,GRAS
● yes [ ] ● no [X] ● Some are cleared, others not [ ]
If yes, the entire formulation is cleared under 21CFR§

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively: ●
yes [X] ● no [ ]

8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

Active ingredient(s)	REG-NO	% by weight NC	UCL	LCL
Imidacloprid	[redacted]			
Pyriproxyfen				

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:
● yes [ ] ● no [X]
Not acceptable for imidacloprid and Pyriproxyfen-as required in PR Notice 91-2

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different: ● yes [ ] ● no [X]
PRODUCT LABEL

11. The chemical names of the active ingredients on the label are identical to those on the CSF: ● yes [X] ● no [ ]

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:
● yes [ ] ● no [ ] ● not applicable [X]

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:
● yes [X] ● no [ ]

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.--	Data Required Fulfilled	MRID No.
1550. Chemical Identity(CSF)	N	450969-02
1600. Beginning Materials 1620. Formulation Process	Y	450969-02
1670. Discussion of Impurities	Y	450969-02
1700. Preliminary Analysis	Y	450969-02
1750. Certified Limits(CSF)	N	450969-02
1800. Enforcement of Analytical Method	Y	450969-01

15. Physical/Chemical Properties New Guideline No. 830.---	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
6303. Physical State	Y	Liquid	450969-03
7300. Density/Bulk Density	Y	1.092 lbs/gal	450969-03
7000. pH	NA	6.02	450969-03
6314. Oxid/Red Action	Y	No ox. Or red. Action	450969-03
6315. Flammability-Flash Point	Y	above 100.2°C	450969-03
6315. Flame Extension	NA		--
6316. Explodability	Y	--	10-27-00 Bayer rebuttal
6317. Storage Stability.	N	--	--
7100. Viscosity	Y	5.13 cSt	450969-03

6319. Miscibility	Y	--	10-27-00 Bayer rebuttal
6320. Corrosion Characteristics	Y	Non-corrosive as packaged, tested for about 30 days	450969-03
6321. Dielectric Breakdown Voltage	Y	---	10-27-00 Bayer rebuttal

Explanations: Y = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

Product ingredient source information may be entitled to confidential treatment

DATE: 22/NOV/2000

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP's [X]

DP BARCODE No.: D270181
REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
AND
DP BARCODE No.: D270183
REG./File Symbol No.: 11556-REI
PRODUCT NAME: Advantage Plus 10 for Dogs
AND
DP BARCODE No.: D270184
REG./File Symbol No.: 11556-REL
PRODUCT NAME: Advantage Plus 20 for Dogs
AND
DP BARCODE No.: D270182
REG./File Symbol No.: 11556-REO
PRODUCT NAME: Advantage Plus 18 for Cats
AND
DP BARCODE No.: D270186
REG./File Symbol No.: 11556-RET
PRODUCT NAME: Advantage Plus 55 for Dogs
AND
DP BARCODE No.: D270188
REG./File Symbol No.: 11556-RGN
PRODUCT NAME: Advantage Plus 100 for Dogs

COMPANY: Bayer Corporation

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch (TRB)/RD (7505C)

TO: Tina Levine/Dani Daniel, PM #4
Insecticide Branch/RD(7505C)

INTRODUCTION

The Bayer Corporation previously applied for registration of six new Advantage Plus insecticides [redacted] intended to kill fleas on different sizes of cats and dogs. The new products differs from the previous ones in that they include an insect growth regulator, pyriproxyfen, to help control flea eggs, and contains an additional inert. TRB

(L. Kutney) reviewed these data on June 2, 2000. All six products contain identical CSFs (dated 4-7-00) and separate proposed labels (dated 4-7-00). This review summarizes the Agency conclusions included in the June 2, 2000, review, Bayer's October 27, 2000, rebuttal to the Agency's conclusions and the Agency's response to Bayer's rebuttal.

Item 1

Agency Conclusion of June 2, 2000

Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical.

Bayer's Rebuttal of October 27, 2000

"The nominal concentrations of a.i.'s on the CSFs and the draft product labels are identical. For example, the upper and lower certified limits for imidacloprid are 9.6% and 8.6%, respectively, and the nominal concentration for imadacloprid is 9.1% on both the CSF and the draft labeling. Please note, the upper, lower and nominal concentrations for imidacloprid are identical to those on the CSFs and labels for the 7 registered Advantage products (EPA Reg. Nos. 11556-116 through 11556-122). For ease of reference, a CSF for Advantage 10, EPA Reg. No. 11556-117, is enclosed. The Confidential Appendix of the review states *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* As 8.9% is not on the CSF, we surmise that this value may have been calculated to correct for percent purity of the technical material. Thus, the nominal concentrations of the a.i.'s on the CSF are identical to the label concentrations, and the CSF and draft labeling for the Advantage Plus products are correct."

Agency Response of November 21

Subpart D-Product Chemistry Data Requirements, May 24, 2000, draft, defines the nominal concentration required by 158.155 as the "amount of active ingredient that is most likely to be present in the product when produced," in other words, the %active ingredient in the product (See also OPPTS 830.155, p.1). In addition, the nominal concentrations on the CSF and the draft label must be identical.

The Agency reiterates that *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45% not 9.10% and 0.46%, respectively as stated on the proposed label."* Bayer is correct in assuming that the nominal concentration of imidacloprid is corrected to account for the fact that technical imidacloprid a.i. [redacted] pure, and technical pyriproxyfen a.i. [redacted] pure. The nominal concentration of each a.i. from the CSF is calculated, as follows:

nominal concentration of the a.i. =

$$\frac{\text{The amount of each a.i. (kg), column 13a}}{\text{Total weight of components in column 13a}} \times (\%\ \text{purity of a.i. technical})$$

Bayer may either make sure that the label stated concentration is adjusted to be identical to the nominal concentrations of the a.i.'s or adjust the amount of each a.i. component so that the nominal concentration of each a.i. is identical to the proposed label concentration.

Item 2

Agency Conclusion of June 2, 2000

The name and address of the suppliers of inerts should be included on a revised CSF.

Bayer's Rebuttal of October 27, 2000

"Bayer acknowledges that the supplier(s) for "specialty" or proprietary materials must be listed on the CSF, but for those chemicals which are considered "commodity" chemicals, Bayer has not routinely listed the suppliers. As examples, the CSF's for the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) do not list the suppliers. The enclosed CSF for Advantage 10, EPA Reg. No. 11556-117, is a specific example. The Agency has permitted this in the past and acknowledges this practice which allows a change in source of these commodity chemicals without notification as permitted under PR Notice 98-10, Section III, B, 1.

As all of the inert ingredients in the proposed formulation for the A Plus products are commodity chemicals and are the same commodity chemicals which are in the Advantage formulation (Reg Nos 11556-116 through 11556-122) for which the Agency did not require the suppliers to be listed, Bayer would prefer not to list the suppliers of these chemicals for the Advantage Plus formulation."

Agency Response of November 21

The Agency routinely requests the names and addresses of suppliers of inerts on CSF's in order to be able to contact the supplier about the contents of their inerts, when necessary. The Instructions to EPA Form 8570-4, for Confidential Statement of Formula, Supplier Name and Address, number 11, specify that the Registrant should, "Provide the name and address of the supplier of each component in the (CSF) formulation. If one or more components will be obtained from more than one source, specify the names and addresses of the alternate sources also." There is no exception for "commodity chemicals."

A revised CSF including the name and address of the suppliers of inerts is still required.

Item 3

Agency Conclusion of June 2, 2000

The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled "Confidential Business Information." This is a 3-97 FIFRA requirement (Section 10 (d)(1))needed for enforcement purposes, etc.

Bayer's Rebuttal of October 27, 2000

"One copy of the method without any "confidential" markings is included with this letter. Please note that this method is to be used for all six product applications.

Agency Response of November 21

An analytical method labeled "CBI" is not permitted as an enforcement method. The Agency acknowledges the receipt of the enforcement analytical method without this label and considers that the requirement for analytical method (40CFR 158.180) is now satisfied.

Item 4

Agency Conclusion of June 2, 2000

Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the Product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

Bayer's Rebuttal of October 27, 2000

Explodability "The OPPTS Test GDL 830.6316 for Explodability states 'The explodability test is necessary for use in precautionary labeling of pesticides when the product is potentially explosive.' Previous Agency guidance ('Roadmap for Guidance to Product Chemistry Guidelines' report from Anne Lindsay...) on this data requirement stated the requirement is for dusts and dusts from granular or powdered products. The Advantage Plus formulation is a liquid formulation. Moreover, it is not potentially explosive. The currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive..."

Agency Response of November 21

Explodability

The Agency is aware that Advantage Plus is a liquid formulation. Section 158.190 of the 40 Code of Federal Regulations states that explodability testing is required if the product is

potentially explosive. However, the requirement for data concerning explodability definitely applies to liquid end use products as well as dusts and dusts from granular or powdered products. In fact, some liquids have a very high explosive potential, e.g., nitroglycerine.

Registrants are obliged to characterize the explodability of new end use products, in the absence of data or documentation to the contrary, the Agency may consider that any new product may be potentially explosive. Bayer has now certified that the currently registered Advantage formulation is not potentially explosive and the Advantage Plus formulation would be even less explosive...due to substitution of substitution of organic some organic solvent with water.

The requirement for explodability testing, OPPTS Test GDL 830.6316, is now satisfied.

Bayer's Rebuttal of October 27, 2000

Storage Stability As stated in 830.1000 Background for Product Properties Test Guidelines for the (viiii) OPPTS 830.6317 Storage Stability discussion on p 17:

- "The requirement for data (storage stability) on the EP applies on when: The product use pattern is one for which performance (efficacy) data are required (40CFR 158.640); the results of the storage stability study indicate that the concentration of any active ingredient is not within the certified limits or degradates of toxicological significance are detected in the study; or product instability is suspected or incidents of instability are reported."

Advantage Plus does not meet any of these conditions, as it is an EP, it is not registered for the use patterns for which efficacy data are required under 40 CFR 158.640, and the product/a. i.'s are known to be stable. Thus, storage stability data for the Advantage Plus formulation should not be required for submission.

Agency Response of November 21

Product Properties Test Guidelines OPPTS 830.6317 (b) for Storage Stability states that, "The objective of storage stability testing is to determine how long the product will retain the percent a.i. in its packaging material corresponding to its useful shelf life. The storage stability study provides data on change (or lack of change) in product composition over time, If certain ingredients decompose, other new chemicals are formed whose toxicity and other characteristics must be considered." Bayer should read 830.6317 for details concerning the requirements for storage stability testing. Storage stability testing is required end-use formulations, including the Advantage Plus formulation.

Bayer's Rebuttal of October 27, 2000

Miscibility GDL 830.6319 for Miscibility states:

- "This test is intended to determine whether a pesticide solution is suitable for application

after dilution with oil or other nonpolar solvents where applicable, instead of water. Data on miscibility also provide necessary information to support acceptable labeling for tank mix and spray applications (if the tank mix of the pesticide product is oil based or diluted with oil)."

Agency Response of November 21

GDL OPPTS 830.6319 for miscibility states, "Data on the physical and chemical characteristics of pesticide products are used to confirm or provide supportive information on their identity. Such data are used in reviewing the production or formulation process to produce the pesticide or product." However, the Agency is willing to concede that, as stated in 40 CFR 158.190 "the miscibility test is required if the liquid is an emulsifiable liquid and is to be diluted with petroleum solvents." Provided there is no alteration of use pattern for Advantage Plus which would involve dilution with petroleum or non-polar solvents, there will be no requirement imposed for miscibility testing.

Bayer's Rebuttal of October 27, 2000

Dielectric Breakdown Voltage

...Advantage Plus is to applied directly to dogs and cats in small volumes...use is not around electric equipment...

Agency Response of November 21

GDL 830.6321 states that dielectric breakdown voltage is required when the pesticide product is used on or in the vicinity of electrical equipment and electrical conduits. Dielectric breakdown voltage will not be required for this product, provided there is no alteration of use pattern which would increase exposure of the pesticide handlers to electrical equipment or electrical conduits.

The requirement for data concerning dielectric breakdown voltage is now satisfied.

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.: D265763 REG./File Symbol No.: 11556-REA
PRODUCT NAME: Advantage Plus 9 for Cats
COMPANY: Bayer Corporation

1 Reviewer: Linda L. Kutney

2. Company: Bayer Corporation

3. Type of Submission: Registration [X] Reregistration [ ] New [X] Resubmission [ ] Amendment [ ] "ME-TOO" [X] Alternate Formulation [ ] Experimental Use Permit [ ] Other (Specify)

4. If "Me-TOO" Registration, this product is [ ] is not [X] similar or substantially similar to EPA's Reg. No.:
11556-116
If not, comment in Confidential Appendix on the significant differences between the registered and the new source.

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
- Non-integrated formulation system.....[X]
- Are all technical grade active ingredients used registered? ● yes [X] ● no [ ], If no, specify
- Integrated formulation system.....[ ]

6. Clearance of intentionally added ingredients in the formulation for the intended use (indicate in the Confidential Appendix those that are not cleared; the PC Codes should be provided by the chemist on the CSF for those that are cleared):

6(a) Formulation intended for food use under 40CFR§180.1001:
● yes [ ] ● no [X] ● Some are cleared, others are not [ ]
Cleared under list: ● c[ ] ● d[ ] ● e [ ]
Are there any limitations for use as an inert under 40CFR§180.1001?

● yes [ ] ● no [X], If yes, specify

6(b) Formulation intended for non-food use:
● yes [X] ● no [ ] ● Some are cleared, others are not [ ]

6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199,e.g.,(a) indirect food additives, such as food contact surface sanitizers; adhesives, coatings, paper and paperboard products that may contact food in packaging or holding; & (b) substances

generally recognized as safe,GRAS
● yes [ ] ● no [X] ● Some are cleared, others not [ ]
If yes, the entire formulation is cleared under 21CFR§

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively: ●
yes [X] ● no [ ]

8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

Active ingredient(s)	REG-NO	% by weight NC	UCL	LCL
Imidacloprid	[redacted]			
Pyriproxyfen				

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:
● yes [ ] ● no [X]
Not acceptable for imidacloprid and Pyriproxyfen-as required in PR Notice 91-2

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different: ● yes [ ] ● no [X]
PRODUCT LABEL

11. The chemical names of the active ingredients on the label are identical to those on the CSF: ● yes [X] ● no [ ]

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:
● yes [ ] ● no [ ] ● not applicable [X]

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:
● yes [X] ● no [ ]

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.--	Data Required Fulfilled	MRID No.
1550. Chemical Identity(CSF)	N	450969-02
1600. Beginning Materials 1620. Formulation Process	Y	450969-02
1670. Discussion of Impurities	Y	450969-02
1700. Preliminary Analysis	Y	450969-02
1750. Certified Limits(CSF)	N	450969-02
1800. Enforcement of Analytical Method	Y	450969-01

15. Physical/Chemical Properties New Guideline No. 830.---	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
6303. Physical State	Y	Liquid	450969-03
7300. Density/Bulk Density	Y	1.092 lbs/gal	450969-03
7000. pH	NA	6.02	450969-03
6314. Oxid/Red Action	Y	No ox. Or red. Action	450969-03
6315. Flammability-Flash Point	Y	above 100.2°C	450969-03
6315. Flame Extension	NA		--
6316. Explodability	Y	--	10-27-00 Bayer rebuttal
6317. Storage Stability.	N	--	--
7100. Viscosity	Y	5.13 cSt	450969-03

6319. Miscibility	Y	--	10-27-00 Bayer rebuttal
6320. Corrosion Characteristics	Y	Non-corrosive as packaged, tested for about 30 days	450969-03
6321. Dielectric Breakdown Voltage	Y	---	10-27-00 Bayer rebuttal

Explanations: Y = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

Bayer

Agriculture Division

Animal Health

Bayer Corporation
P.O. Box 390
Shawnee Mission, KS 66201-0390
Phone: 913 268-2000

via Federal Express

October 27, 2000

Ms. Dani Daniel
Registration Division (H7505C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Response to Product Chemistry Review for Advantage® Plus 9, 18, 10, 20, 55, and 100 Products (EPA File Symbols 11556-REO, -REA, -REI, -REL, -RET, -RGN)

Dear Ms. Daniel:

Bayer Corporation received product chemistry reviews (dated June 16, 2000) from the Agency on June 22, 2000 for the six products referenced above. The reviews stated that product labels and confidential statements of formula (CSFs) contain a number of deficiencies that need to be addressed. In addition, you requested that we should make no label changes until the entire package (domestic animal safety and acute toxicity) has been reviewed. The following is Bayer's response to the Agency's product chemistry reviews. Please note that the same deficiencies were identified by the reviewer for all six products as the formulation and nominal label concentrations are the same for all six products.

The deficiencies and Bayer's responses are detailed below.

Item 1

Agency conclusion: *"Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical."*

Bayer response: The nominal concentrations of a.i.'s on the CSFs and the draft product product labels are identical. For example, the upper and lower certified limits for imidacloprid are 9.6% and 8.6%, respectively, and the nominal concentration for imidacloprid is 9.1% on both the CSF and the draft labeling. Please note, the upper, lower and nominal concentrations for imidacloprid are identical to those on the CSF's and labels for the 7 currently registered Advantage products (EPA Reg. Nos. 11556-116

through 11556-122). For ease of reference, a CSF for Advantage 10, EPA Reg. No. 11556-117, is enclosed. The Confidential Appendix of the review states *"The CSF for the subject product contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45%, not 9.10% and 0.46%, respectively as stated on the proposed label."* As 8.9% is not on the CSF, we surmise that this value may have been calculated to correct the CSF values for the percent purity of the active ingredients. However, the active ingredient values listed on the CSF have already been corrected for percent purity of the technical material. Thus, the nominal concentrations of the a.i.'s on the CSF are identical to the label concentrations, and the CSF and draft labeling for the Advantage Plus products are correct.

Item 2 Agency conclusion: *"The name and address of the suppliers of inerts should be included on a revised CSF."*

Bayer response: Bayer acknowledges that the supplier(s) for "specialty" or "proprietary" materials must be listed on the CSF, but for those chemicals which are considered "commodity" chemicals, Bayer has not routinely listed the suppliers. As examples, the CSF's for the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) do not list the suppliers. The enclosed CSF for Advantage 10, EPA Reg. No. 11556-117 is a specific example. The Agency has permitted this in the past and acknowledges this practice which allows a change in a source of these commodity chemicals without notification as permitted under PR Notice 98-10, Section III, B, 1.

As all of the inert ingredients in the proposed formulation for the Advantage Plus products (EPA File Symbols 11556-REO, -REA, -REI, -REL, -RET, and -RGN) are commodity chemicals and are the same commodity chemicals which are in the Advantage formulation (EPA Reg. Nos. 11556-116 through 11556-122) for which the Agency did not require the suppliers to be listed, Bayer would prefer not to list the suppliers of these chemicals for the Advantage Plus formulation.

Item 3 Agency conclusion: *"The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled 'Confidential Business Information.' This is a 3-97 FIFRA requirement (Section 10 (d)(1)) needed for enforcement purposes, etc."*

Bayer response: One copy of the method without any "confidential" markings is included with this letter. Please note that this method is to be used for all six product applications.

Item 9 Agency conclusion: *"Group B product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), storage stability of the product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted."*

Bayer response: These tests are not required under 40CFR 158.190 or PR Notice 92-5. Each item is discussed in detail below.

Explodability. The OPPTS Test Guideline 830.6316 for Explodability states, "The explodability test is necessary for use in precautionary labeling of pesticides when the product is potentially explosive." Previous Agency guidance ("Roadmap for Guidance to Product Chemistry Guidelines" report from Anne E. Lindsay, Director of the Registration Division, to Margaret Stasikowski, Deputy Director of Special Review and Reregistration Division) on this data requirement stated the requirement is for dusts and dusts from granular or powdered products. The Advantage Plus formulation is a liquid formulation. Moreover, it is not potentially explosive. The currently registered Advantage formulation is not potentially explosive, and the Advantage Plus formulation would be even less explosive as the formulation is very similar to the Advantage formulation in that some of the organic solvent has been removed and substituted with water and 0.46% pyriproxyfen which is not explosive.

Storage Stability. As stated in the OPPTS 830.1000 Background for Product Properties Test Guidelines for the (viii) OPPTS 830.6317 Storage Stability discussion on page 17:

> "The requirement for data (storage stability) on the EP applies on when: The product use pattern is one for which performance (efficacy) data are required (40 CFR 158.640); the results of the storage stability study indicate that the concentration of any active ingredient is not within the certified limits or degradates of toxicological significance are detected in the study; or product instability is suspected or incidents of instability are reported."

Advantage Plus does not meet any of these conditions, as it is an EP (end-use product), it is not registered for the use patterns for which efficacy data are required under 40 CFR 158.640, and the product/active ingredients are known to be stable. Thus, storage stability data for the Advantage Plus formulation should not be required for submission.

Miscibility. The OPPTS Test Guideline 830.6319 for Miscibility states:

> "This test is intended to determine whether a pesticide solution is suitable for application after dilution with oil or other nonpolar solvents, where applicable, instead of water. Data on miscibility also provide necessary information to support acceptable labeling for tank mix and spray applications (if the tank mix of the pesticide product is oil, based or diluted with oil)."

The Advantage Plus formulation is a ready-to-use liquid for direct application in small amounts (no greater than 4.0 ml) directly to dogs or cats. The Advantage Plus formulation is not to be diluted with any material and obviously is not intended for tank mix and spray applications. Thus, miscibility data are not applicable and should not be required for the Advantage Plus formulation.

Dielectric Breakdown Voltage. The OPPTS Test Guideline 830.6321 for Dielectric Breakdown Voltage states the following:

> "The objective of this test is to determine the potential for hazard when the pesticide product is used on or in the vicinity of electrical equipment and electrical conduits. The dielectric breakdown voltage of an insulating liquid is of importance as a measure of the liquid's ability to withstand electric stress without failure. Data is required when the end-use product is a nonconductant liquid and is to be used around electrical equipment."

The Advantage Plus formulation is to be applied directly to dogs and cats in small volumes (again, never more than 4.0 ml even with the largest animals). Clearly this use is not around electric equipment, and thus, these data are not applicable and should not be required for the Advantage Plus formulation.

With the enclosed enforcement method and rationale for not needing testing for explodability, storage stability, dielectric breakdown voltage and miscibility, all the Agency's requirements for product chemistry for the Advantage® Plus products (EPA File Symbols 11556-REO, -REA, -REI, -REL, -RET, -RGN) should be fulfilled.

Please call me at (913) 268-2751 if you have any questions or need additional information.

Sincerely,

Gregory G. Gagliano
Manager, Environmental Research

GGG/lt

Enclosures

1.0 SCOPE

Applicable to samples of the Imidacloprid (10% w/v, 9.1% w/w)/Pyriproxyfen (1% w/v, 0.9% w/w or 0.5% w/v, 0.46% w/w) Topical solution formulations.

2.0 PRINCIPLE/SUMMARY

The imidacloprid/pyriproxyfen formulation is dissolved and diluted with an acetonitrile/phosphate buffer diluent to reduce the concentration to give responses in the linear range of the detector. The solutions are analyzed by reversed-phase high performance liquid chromatography (HPLC) with UV absorbance detection at 230 nm. The concentrations of the analytes are determined, using peak area data, by external standard calculation and single-point calibration with a known standard.

3.0 REFERENCES

3.1 TMA 5.15, "Specific Gravity of Liquids by DMA-45"
3.2 PRD820, "Chromatographic Analysis - R&D"
3.3 PQC839, "Chromatographic Analysis in Pharmaceutical QC"
3.4 MD204, "Validation of Chromatographic Analytical Test Methods"

4.0 REAGENTS

4.1 Acetonitrile, HPLC grade
4.2 Water, HPLC grade
4.3 Phosphoric acid 85%, reagent grade
4.4 Potassium phosphate, monobasic, reagent grade
4.5 Imidacloprid analytical standard of known purity
4.6 Pyriproxyfen analytical standard of known purity
4.7 Buffer - Scale the preparation as required. For 1 L of buffer, dissolve 1.36 g of potassium phosphate monobasic in 1 L of HPLC grade water. Adjust the pH to 3.0 with phosphoric acid (approximately 0.1 mL).
4.8 Diluent - Scale the preparation as required. Combine 650 mL of buffer with 350 mL of acetonitrile, mix thoroughly, and filter.
4.9 Pump A - mobile phase - Scale the preparation as required. Combine 900 mL of buffer with 100 mL of acetonitrile, mix thoroughly, filter and degas.
4.10 Pump B - mobile phase - Scale the preparation as required. Combine 150 mL of buffer with 850 mL of acetonitrile, mix thoroughly, filter, and degas.

5.0 APPARATUS/MATERIALS/SUPPLIES

5.1 Analytical balance
5.2 High Performance Liquid Chromatograph (HPLC) equipped with a column oven, binary gradient capability, and a UV detector capable of monitoring absorbance at 230 nm.
5.3 Autosampler with a 20 µL injection capacity.
5.4 Column - Nucleosil C18, 5 µm particle size, 120-angstrom pore size, 125 x 4-mm.
5.5 Vacuum filtration apparatus.
5.6 Gelman Nylaflo membrane filters, 0.45 µm pore size.

5.7 Glassware - 50, 100 and 250 mL class A volumetric flasks and 10 mL class A volumetric pipets.

6.0 PROCEDURE

6.1 Standard Preparation

1. Transfer approximately 0.070 g (accurately weighed to ± 0.0001 g) for 1% pyriproxyfen analytical standard to a 100 mL volumetric flask. Dissolve and dilute to volume with acetonitrile.

2. Transfer approximately:
   - 0.070 g (accurately weighed to ±0.0001 g) for 1% pyriproxyfen formulations of imidacloprid analytical standard to a 250 mL volumetric flask.
   - 0.140 g (accurately weighed to ±0.0001 g) for 0.5% pyriproxyfen formulations of imidacloprid analytical standard to a 250 mL volumetric flask.

   Dissolve with approximately 75 mL of diluent. Transfer 10 mL of the solution from step 6.1.1 to the flask, dilute to volume with diluent, and mix thoroughly.

6.2 Sample Preparation

1. For 1% (w/v) pyriproxyfen formulations:
   Transfer approximately 0.140 g (accurately weighed to ±0.0001 g) of sample to a 50 mL volumetric flask. Dissolve and dilute to volume with diluent.

2. For 0.5% w/v pyriproxyfen formulations:
   Transfer approximately 0.280 g (accurately weighed to ±0.0001 g) of sample to a 50 mL volumetric flask. Dissolve and dilute to volume with diluent.

6.3 Chromatographic Analysis

1. Set the following instrumental conditions:

Injection volume	20 µL
Wavelength	230 nm
Temperature	40°C
Run Time	53 minutes

Gradient program: (The gradient ramps are linear)

Time (min)	Flow (mL/min)	%B
0	1.0	10
13.5	1.0	10
17.0	1.0	58
29.5	1.0	58
30.0	1.0	73
39.0	1.0	73
39.5	1.0	100

Time (min)	Flow (mL/min)	%B
42.0	1.0	100
42.5	2.0	10
51.0	2.0	10
51.1	1.0	10

2. Obtain a stable baseline before making an injection.

3. Proceed according to PQC-839 (QC) or PRD-820 (R&D) except for sections 4.1 and 4.4.

4. Compare the retention times of imidacloprid and pyriproxyfen in the analytical standard chromatogram to those in the sample chromatogram. The retention times should be similar for pyriproxyfen (±0.1 min for imidacloprid, ±0.4 min for pyriproxifen). Typical chromatograms are shown in Figures 1 and 2.

7.0 CALCULATIONS

Determine the % imidacloprid and % pyriproxyfen in the sample by comparison of the respective peak areas from the sample chromatogram to those from the standard chromatogram.

$$K = \frac{W_{std} \times P}{A_{std}}$$

$$\%\ (w/w)\ analyte = \frac{A_{spl} \times K \times F}{W_{spl}}$$

$$\%\ (w/v)\ analyte = \frac{A_{spl} \times K \times F \times d}{W_{spl}}$$

W_{std} = Weight of the analytical standard (g).
P = Percent purity of the analytical standard.
A_{std} = Area of the analyte peak in the standard chromatogram.
A_{spl} = Area of the analyte peak in the sample chromatogram.
F = Dilution factor: 0.2 for imidacloprid, 0.02 for pyriproxyfen.
W_{spl} = Weight of the sample (g).
d = Density of the sample (g/mL).

8.0 INTERPRETATION OF RESULTS

The results should meet Bayer specifications. If not, notify the supervisor.

9.0 VALIDATION

This method was validated for the 1% w/v (0.91% w/w) pyriproxyfen formulation and the results of the validation are presented in a Bayer Animal Health report 74889. Validation for other formulations will be in Report No. 75130.

REASON TO ISSUE: To update Figures 1 and 2, typical chromatograms.

Chris Bosel 11/23/99

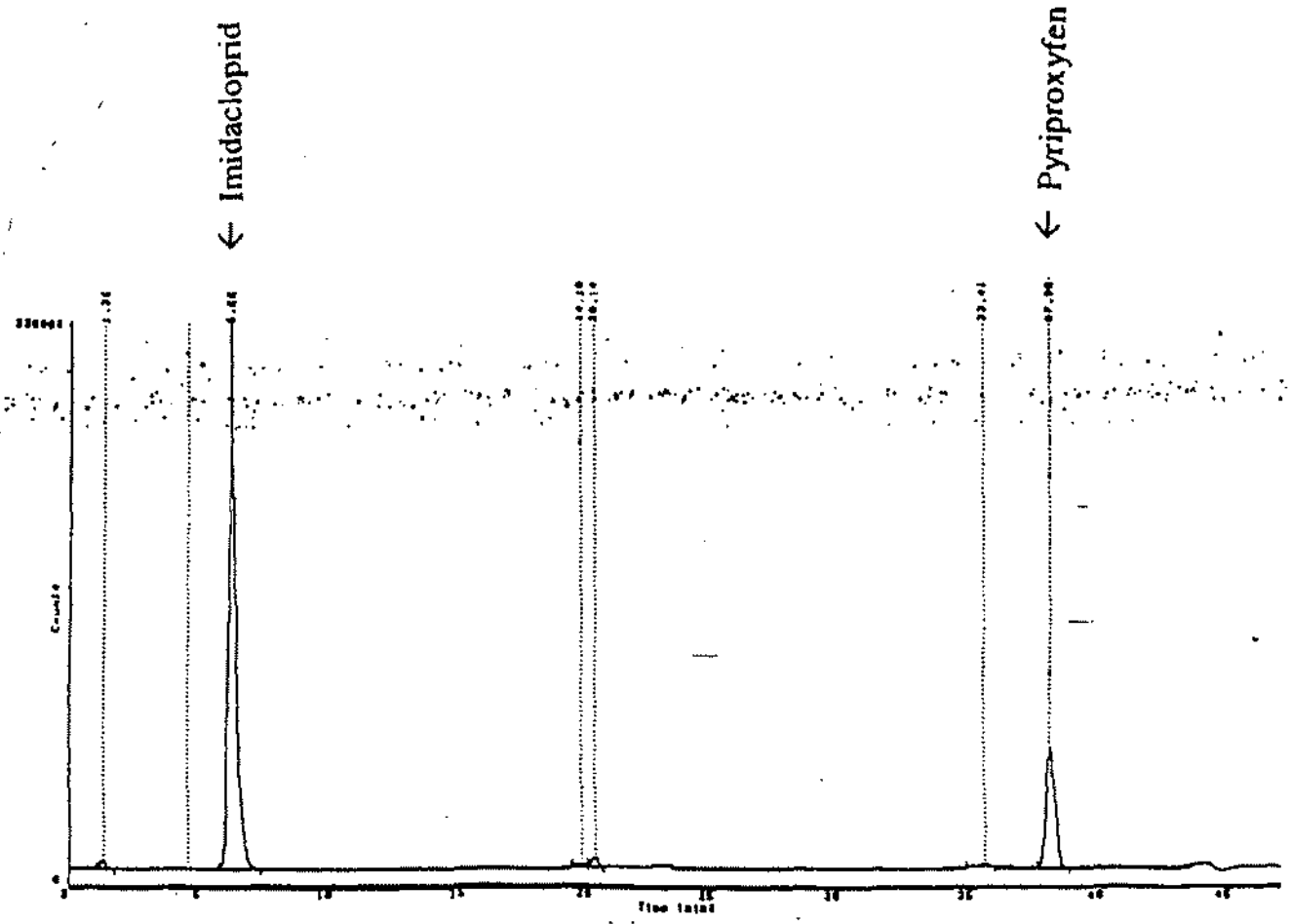
Pharmaceutical R & D Date

23-Nov-99

Quality Assurance Date

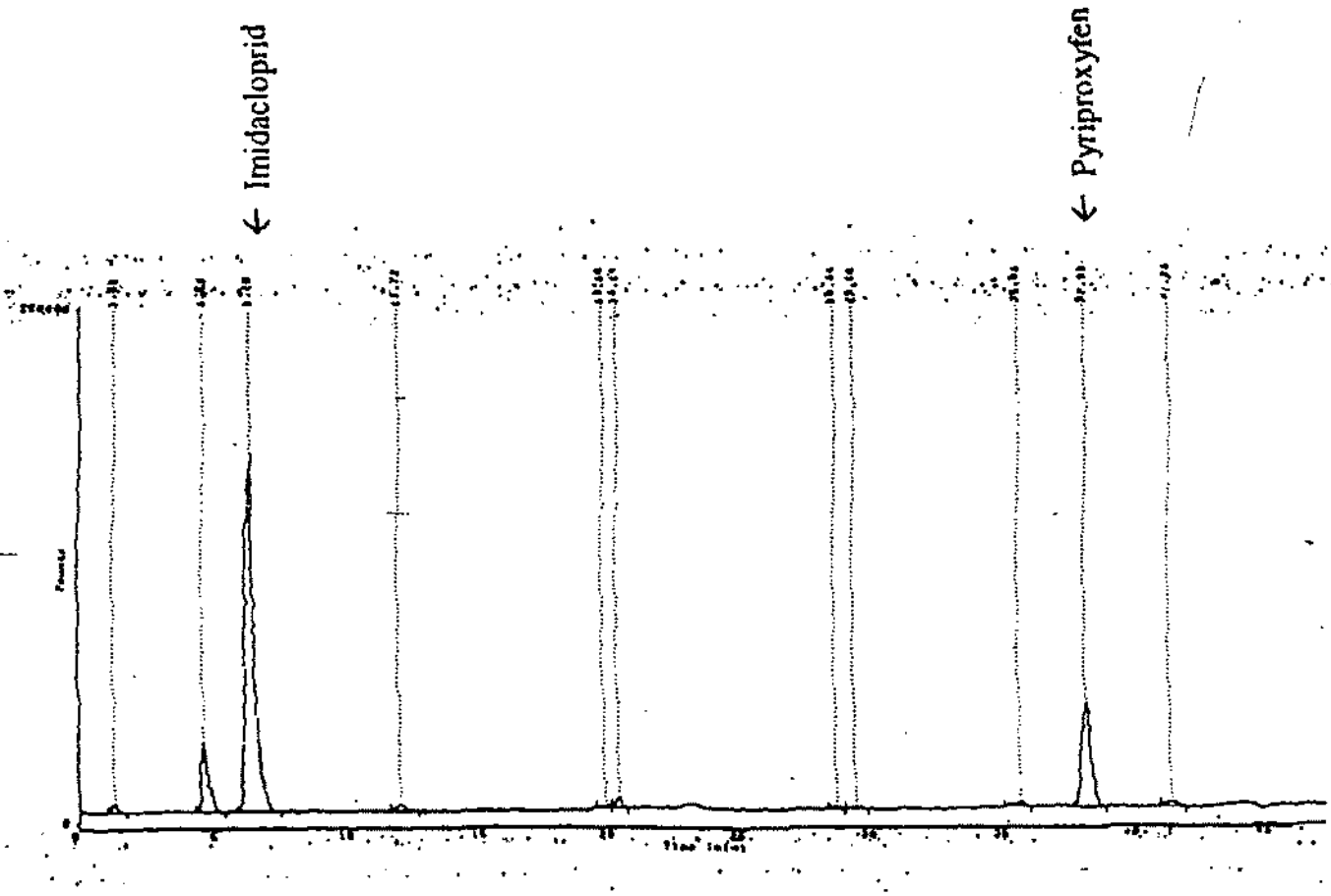
TYPICAL STANDARD CHROMATOGRAM

Figure 1



TYPICAL SAMPLE CHROMATOGRAM

Figure 2



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OCT 5 2000

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Applications for New Advantage Products
Reg. No. 11556-REA, REO, REI, REL, RET, RGN
Your submission date, April 7, 2000

Dear Mr. McNamara:

Enclosed are the final two animal safety study reviews, for registration numbers 11556-REA and REO. You should now have complete package. If you are missing any reviews, please let me know.

The labeling referred to above, submitted in connection with the above registrations under the Federal Insecticide, Fungicide, and Rodenticide Act is not acceptable for the reasons below:

As indicated in my June 16, 2000, letter a number of deficiencies exist with your labels and confidential statements of formula that need to be corrected before a registration can be given. The following are deficiencies are can be found in the product chemistry review:

1. The proposed labels should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable:

-technical information on symptomatology;
-use of supportive treatments to maintain life functions;
-medicine that will counteract the specific physiological effects of the pesticide;
-company telephone number to specific medical personnel who can provide specialized medical advice.

2. Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the

concentrations of the a.i.'s are correct and identical.

3. The name and address of the suppliers of inserts should be included on a revised CSF.

4. The enforcement analytical method will be satisfactory, providing the Registrant submits a new copy not labeled "confidential Business Information." This is a 3-97 FIFRA requirement (Section 10(d)(1) needed for enforcement purposes, etc.

5. Group B product chemistry requirements listed in series 830 guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

6. None of the subject products are substantially similar to any of the parent products from a product chemistry point of view, because they each contain an additional a.i. and inert ingredient, and because the nominals and certified limits of the components are not substantially similar.

Please read the reviews and make changes as specified. Upon making the changes, please resubmit your labels and CSFs. If there are question, call me at 703 305-5409.

Sincerely,

/S/

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-Way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

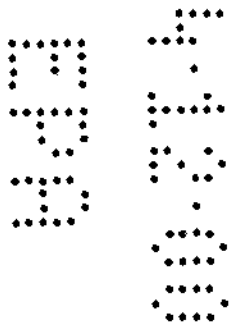
Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

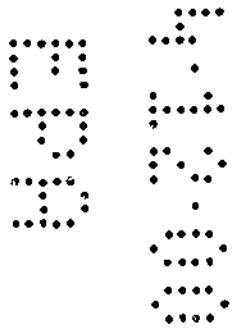
Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

READ ENTIRE LABEL BEFORE EACH USE



(Leaflet)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment for Dogs and
Puppies 7 Weeks and Older and 10 lbs and Under

READ ENTIRE LABEL BEFORE USE

For the Prevention and Treatment of Flea Infestation on Dogs.

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

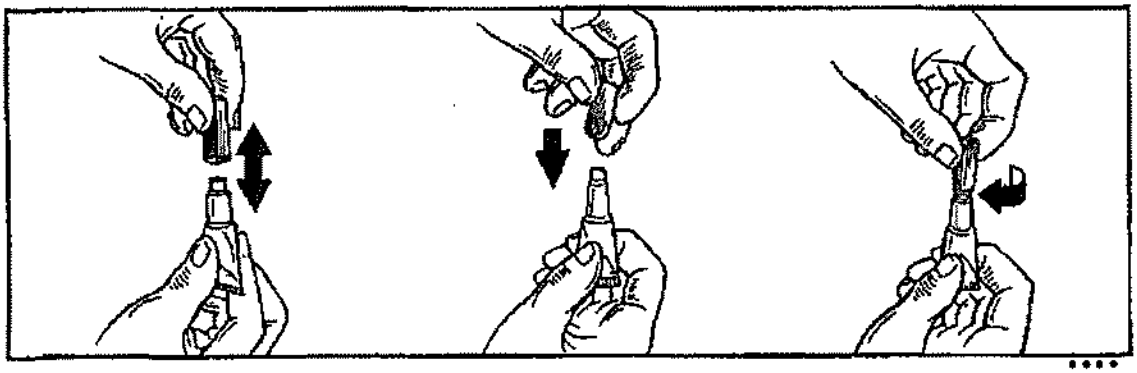
To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY

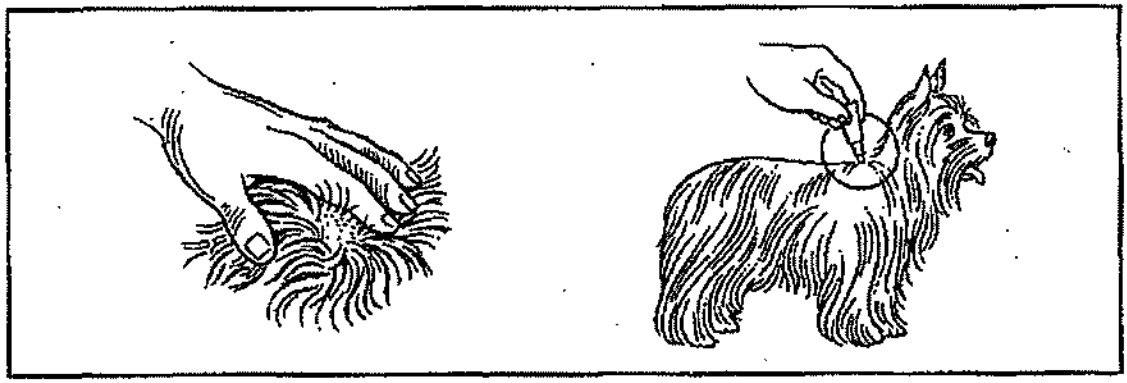
1. Use only on dogs. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

   Do not get this product in your pet's eyes or mouth.



7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal**: Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal**: Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

EPA Est. 11556-DEU-1

EPA Reg. No. 11556-~~XXX~~ REI

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SEP 18 2000

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Applications for New Advantage Products
Tox and Animal Safety Studies
Reg. No. 11556-REI, RET, REL
Your submission date, April 7, 2000

Dear Mr. McNamara:

Just a note to let you know that we are coming to a close with reviewing your six new product applications for Advantage. Enclosed is a copy of three completed animal safety study reviews. To complete the reviews, two animal safety study reviews are need. Upon completion, I will notify you as to when you can commence with label changes needed to satisfy registration of your products. If there are questions, call me 703 305-5409.

Sincerely,

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

September 8, 2000

MEMORANDUM

EPA File Symbol: 11556-REI Advantage® Plus 10 for Dogs
DP Barcode: D265774
Case No: 068809
Submission: S579325
PC Codes: 129099 Imidacloprid; 129032 Pyriproxyfen

From: Byron T. Backus, Ph.D., Toxicologist/**s/**
Technical Review Branch
Registration Division (7505C)

To: Helene Daniel/Tina Levine, PM 04
Insecticide-Rodenticide Branch
Registration Division (7505C)

Registrant: BAYER CORP.

ACTION REQUESTED: Review two companion animal (adult dog and puppy) studies on a formulation containing 9.1% Imidacloprid and 0.9% Pyriproxyfen. It is noted that the label for the proposed product has an active ingredient declaration of 9.1% Imidacloprid and 0.46% Pyriproxyfen. The MRID numbers of the two studies are 45097101 (puppy) and 45097102 (dog).

COMMENTS AND RECOMMENDATIONS:

1. Both the puppy study (MRID 45097101) and the adult dog study (MRID 45097102) have been classified as acceptable. For both studies, the lack of any indications of a consistent toxicological response following exposures (4 in each study) to 5X levels of the label-specified application rates indicates that an adequate safety margin exists for this formulation and its proposed use on puppies 7 weeks and older as well as adult dogs. These studies, together with the previously submitted acute toxicity studies, adequately address the toxicity data requirements for this proposed product.

2. In a previous TRB memorandum (Aug. 30, 2000, DP Barcode D265773) it was stated that 11556-REI Advantage® Plus 10 for Dogs has the following acute toxicity profile:

Acute Oral LD50	III
Acute Dermal LD50	IV
Acute Inhalation LC50	IV
Primary Eye Irritation	III
Primary Dermal Irritation	IV
Dermal Sensitization	No

3. All studies (the six acutes, reviewed in the TRB memorandum of Aug. 30, 2000, as well as the puppy and dog companion animal safety studies) were conducted on a formulation containing 9.1% Imidacloprid and 0.9% Pyriproxyfen. The proposed product has a label declaration of 9.1% Imidacloprid and 0.46% Pyriproxyfen, with 90.44% inert ingredients.

4. The proposed application rate to dogs and puppies (7 weeks and older) weighing less than 10 lbs is 0.4 mL product/dog with monthly treatments for optimal control of fleas, but "If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly."

5. As previously noted (TRB memorandum of Aug. 30, 2000), since the Oral LD_{50} value is below 1500 mg/kg, and this product has residential uses, it will require Child Resistant Packaging (CRP).

6. The precautionary labeling for this product, based on the acute toxicity profile and as obtained from the Label Review System, is given in the TRB memorandum dated Aug. 30, 2000.

7. The following is the executive summary from the review for the study on adult dogs in MRID No. 45097102:

> In a companion animal safety study (MRID 45097102) with adult beagles (ages ranging from 1 year and 3 months to 6 years), Advantage Plus® for Dogs (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w) was applied topically at dose volumes of 5.0 mL for dogs weighing 11-20.4 lbs and 12.5 mL for dogs weighing 20.5-55 lbs.(five times the recommended dose) to groups of 6 male and 6 female dogs. Eight dogs were consistently dosed with 12.5 mL of the formulation/application, and four were consistently dosed with 5 mL/application. Controls were dosed with the vehicle at dose volumes of 5.0 mL for dogs weighing 11-20.4 lbs and 12.5 mL for dogs weighing 20.5-55 lbs.(5.6 times the volume of the vehicle present in the recommended dose). Five dogs were consistently treated with 12.5 mL vehicle/application, five were consistently dosed with 5 mL/application, and two dogs received 12.5 mL/application for the first, second and fourth applications, and 5.0 mL/application for the third application. Dogs were treated on study days 0, 7, 14, and 21.
>
> There were no deaths during the study. The dogs received no concomitant medication or therapy during the treatment period. The most prominent clinical sign was a rough appearance of the hair coats on dogs from both groups following

treatment and lasting for up to 36 hours; however, there were no signs of irritation at the application sites. Several dogs from both groups, "jumped excessively due to excitement" on study day 21. The study report did not indicate which dogs. Three dogs (two from the test substance group and one from the vehicle control group) also exhibited sore footpads on that date. These findings for day 21 were not noted at any other time during the study. There were no treatment related effects on body weights, food consumption, or clinical pathology parameters.

It is also noted that the proposed products (containing approximately 9% Imidacloprid, but only 0.46% pyriproxyfen, rather than the 0.9% in the formulation as tested) are similar to existing registered products containing 9% Imidacloprid as sole active. Pyriproxyfen is known to have a low toxicity to mammalian species.

The study is classified as **Acceptable/Guideline** as a companion animal safety study (OPPTS 870.7200) in dogs. The lack of any consistent indications of a toxicological response following exposures (a total of 4) to 5X label-specified use applications of the test material indicates that an adequate safety margin exists for this formulation and its proposed use on adult dogs.

8. The following is the executive summary from the review for the study on beagle puppies (7 weeks old at the time of first treatment) in the study in MRID No. 45097101:

In a companion animal safety study (MRID 45097101), Advantage Plus® for Dogs (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w) was applied topically at a dose of 2.0 mL/puppy (5X the label specified dose of 0.4 mL/puppy for puppies ≤10 lbs) to a group of 7 male and 7 female beagle puppies, seven weeks of age at the time of first treatment. Individual weights of the puppies in the treatment group ranged from 2.54 to 4.01 lbs (1.15-1.82 kg) on day -1. Controls (7M, 7F; weight range: 2.49-5.03 lbs; 1.13-2.29 kg) were dosed with the vehicle alone at a dose of 2.0 mL/puppy (5.6X the volume of the vehicle present in the specified dose). Both groups were treated on study days 0, 7, 14, and 21. The recommended label dose is once a month. However, the labeling for these products includes the statement: "If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly."

There were no deaths during the study. Following all treatments, a rough hair coat condition at the application site was noted on 3-14 puppies of both groups, and white powder was occasionally noted at the application sites; however, there were no signs of irritation. One puppy from the test substance group was found to have ocular discharge and "crusty patches" on its ventral abdomen, by the lip and under each eye on study day 36. The puppies completed treatment for coccidiosis on study day -8. During the remainder of acclimation, in the test substance group there were two observations of loose feces with mucous and five observations of diarrhea, with or without mucous or red colored mucous, exhibited by four animals. In the vehicle control group, there were two observations of loose feces with mucous, exhibited by

two animals.

During the treatment/observation period, in the vehicle control group, there were seven observations of diarrhea (including one with blood) exhibited by 5 animals, and in the test substance group, there were 2 observations of diarrhea, 4 observations of loose feces with mucous (all four of these observations were made on a single female on day 14 post-application), and one observation of only red mucous. It is noted that there was an increased incidence of loose stools in a considerable number of animals (in both treatment groups) following the second (day 14) treatment. In the test material group, 6/14 puppies had loose stools (one with mucous) at one or more times on day 14 following treatment; only one of these puppies had shown this symptom on day 14 prior to treatment. In the vehicle control group, 5/14 puppies had loose stools after treatment; none had shown this symptom on day 14 before treatment. This was not observed on treatment days 7 and 21, and an examination of the data for day 0 indicates the 3/14 puppies in the test material group showing this symptom after treatment had also shown it before treatment on that day, whereas the 3/14 in the vehicle control group showing this symptom had it only after treatment. Mean leukocyte counts were slightly elevated on study days 1 and 22 for the test substance group and on study day 1 for the vehicle control group, and the mean neutrophil count for the test substance group was also slightly elevated on study day 1; however, the mean neutrophil count for all puppies on the study was slightly elevated on day -1 (preexposure) as was the leukocyte count. There were no treatment related effects on body weights or food consumption.

The guideline states that animals should be free from infectious diseases which could complicate the interpretation of study results. It is concluded that, while marginal (in the vehicle control group there were 7 observations of diarrhea - one with blood - exhibited by 5 animals, and in the test substance group there were 2 observations of diarrhea in 2 separate females, 4 observations of loose feces with mucous made on a single female on day 14 post-dosing, and one observation of red mucous, exhibited by a male on day 22) these incidences are low enough that we can consider the study not to be compromised. In addition, the puppies had adequate weight gains during the treatment period. Overall, it appears that the puppies were infected when they arrived at the laboratory but were adequately treated. In addition, they may have been under some stress. The Agency recognizes the difficulties inherent in conducting this type of study under these circumstances, particularly when treatment has to be initiated when the animals are no more than seven weeks old and there are severe scheduling constraints.

It is also noted that this formulation is similar to those of a number of existing registered products, except for the addition of 0.9% pyriproxyfen for efficacy against flea eggs. Pyriproxyfen is known to have extremely low toxicity (both acute and chronic) to mammalian species. In addition, the proposed products which this study is supporting contain 0.46% pyriproxyfen, rather than 0.9%.

Despite the fact that the puppies may not have been entirely free of infection, and

despite some deficiencies in the reporting of the data, the study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) in puppies. The lack of any indications of a consistent toxicological response following exposures (a total of 4) to 5X label-specified use applications of the test material indicates that an adequate safety margin exists for this formulation and its proposed use on puppies 7 weeks of age and older.

DATA EVALUATION REPORT

ADVANTAGE PLUS® 10, 20, 55, AND 100 FOR DOGS
[9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation]

STUDY TYPE: Companion Animal Safety - Dog (OPPTS 870.7200)
MRID 45097102

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
Donna L. Fefee, D.V.M.,
Signature: _____
Date: _____

Secondary Reviewers:
Cheryl B. Bast, Ph.D., D.A.B.T.
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Disclaimer

This review may have been altered subsequent to the contractors signatures above.

Oak Ridge National Laboratory, Managed and Operated by UT-Battelle, LLC, for the U.S. Department of Energy under contract number DE-AC05-00OR22725.

EPA Reviewer:Byron T. Backus, Ph.D. _____ Date: _____

EPA Work Assignment Manager:John Redden, M.Sc: _____ Date: _____
Registration Division (7505C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Dogs [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODES: D265771, D265774, D265778, D265784; MRID NUMBER: 45097102

TEST MATERIAL: Advantage Plus® 10, 20, 55, and 100 for Dogs

STUDY NUMBER: 75121 (150.852)

TESTING FACILITY: Bayer Corporation, Agriculture Division, Animal Health, DeSoto Research Facility, 35040 West 87th Street, Building Number 20, DeSoto, Kansas 66018

SPONSOR: Bayer Corporation, Agriculture Division, Animal Health

TITLE OF REPORT: Evaluation of the general safety of 9.1% (w/w) imidacloprid with 0.9% (w/w) pyriproxyfen spot-on formulation in the target species, adult dog

AUTHOR: A.S. Abraham, B.V.Sc., Ph.D.

REPORT ISSUED: April 4, 2000

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 45097102) with adult beagles (ages ranging from 1 year and 3 months to 6 years), Advantage Plus® for Dogs (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w) was applied topically at dose volumes of 5.0 mL for dogs weighing 11-20.4 lbs and 12.5 mL for dogs weighing 20.5-55 lbs.(five times the recommended dose) to groups of 6 male and 6 female dogs. Eight dogs were consistently dosed with 12.5 mL of the formulation/application, and four were consistently dosed with 5 mL/application. Controls were dosed with the vehicle at dose volumes of 5.0 mL for dogs weighing 11-20.4 lbs and 12.5 mL for dogs weighing 20.5-55 lbs.(5.6 times the volume of the vehicle present in the recommended dose). Five dogs were consistently treated with 12.5 mL vehicle/application, five were consistently dosed with 5 mL/application, and two dogs received 12.5 mL/application for the first, second and fourth applications, and 5.0 mL/application for the third application. Dogs were treated on study days 0, 7, 14, and 21.

There were no deaths during the study. The dogs received no concomitant medication or therapy during the treatment period. The most prominent clinical sign was a rough appearance of the hair coats on dogs from both groups following treatment and lasting for up to 36 hours; however, there were no signs of irritation at the application sites. Several dogs from both groups, "jumped excessively due to excitement" on study day 21. The study report did not indicate which dogs. Three dogs (two from the test substance group and one from the vehicle control group) also exhibited sore footpads on that date. These findings for day 21 were not noted at any other time during the study. There were no treatment related effects on body weights, food consumption, or clinical pathology parameters.

It is also noted that the proposed products (containing approximately 9% Imidacloprid, but only 0.46% pyriproxyfen, rather than the 0.9% in the formulation as tested) are similar to existing registered products containing 9% Imidacloprid as sole active. Pyriproxyfen is known to have a low toxicity to mammalian species.

The study is classified as **Acceptable/Guideline** as a companion animal safety study (OPPTS 870.7200) in dogs. The lack of any consistent indications of a toxicological response following exposures (a total of 4) to 5X label-specified use applications of the test material indicates that an adequate safety margin exists for this formulation and its proposed use on adult dogs.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. Test material

9.1% (w/w) Imidacloprid with 0.9% (w/w) Pyriproxyfen Spot-on Formulation
(Advantage Plus® 10, 20, 55, and 100 for Dogs)
Description: not provided
Lot No.: 99-901-66
Active Ingredients: Imidacloprid, 9.1% (w/w); Pyriproxyfen, 0.9% (w/w)
Storage Conditions: in the dark in a closed cabinet at room temperature.

B. Administration: Topical (spot-on)

C. Vehicle

This consisted of the inert ingredients in the proposed product less the active ingredients.

D. Test animals

Species: Dog
Breed: Beagle

Age and weight at study initiation: 15 months-6 years; males: 6.2-12.9 kg; females: 7.9-14.9 kg
Source: Harlan Sprague Dawley, Inc., P.O. Box 29176, Indianapolis, Indiana 46229
Housing: Individually in runs of approximately 36 square feet and greater than 6 feet high.
Diet: Commercial food (Harlan Teklad, Madison, Wisconsin), once daily
Water: Potable water, *ad libitum*
Environmental conditions:
Temperature: not reported
Humidity: not reported
Air changes: not reported
Photoperiod: not reported
Acclimation period: 14 days

II. STUDY DESIGN

A. In life dates: start: August 10, 1999; end: September 16, 1999

B. Animal assignment/ dosage and administration

Dogs were assigned to the groups in Table 1 using stratified blocked randomization according to weight. Group 1 received the test substance, and group 2 received the vehicle without the two active ingredients at a volume equivalent to the 5X use rate volume of the test substance. The dose volume was 5.0 mL for dogs of either group weighing 11-20.4 pounds and 12.5 mL for dogs of either group weighing 20.5-55 pounds. Treatments were applied to three or more application sites on the top of the back, from the shoulder to the base of the tail. Animals were dosed on Study Days 0, 7, 14, and 21. Dose volumes for treatments on study days 0 and 7 were determined using body weights from study day -1, and dose volumes for treatments on study days 14 and 21 were determined using body weights from study day 13.

TABLE 1. Study design

Group	Number of animals		Dose volume (mL)/multiple of recommended dose		Number of applications[a]
	Male	Female	Body weight 11-20.4 lbs	Body weight 20.5-55 lbs	
1. Test substance	6	6	5.0 mL/5X	12.5mL/5X	4
2. Vehicle control	6	6	5.0 mL/5.6X	12.5mL/5.6X	4

Data taken from pp. 12-13, 16-17 MRID 45097102.
[a] Treatments were given on Days 0, 7, 14, and 21.

C. Dose selection rationale

The study was conducted as a limit test using 5 times the recommended dose volume. The product is dosed by volume according to weight in the following pre-measured dose volumes: 0.4 mL for dogs weighing ≤10 lbs., 1.0 mL for dogs weighing11-20 lbs., 2.5 mL for dogs weighing 21-55 lbs., and 4.0 mL for dogs weighing greater than 55 lbs. Dogs on the study weighing 11-20.4 lbs received 5.0 mL doses, and dogs weighing 20.5-55 lbs. received 12.5 mL doses. All dogs on the study fell into these two weight ranges. The vehicle control group received the vehicle at dose volumes equal to 5 times the recommended use volumes of the test substance, equivalent to 5.6 times the usual use volumes of the vehicle. The product is intended for once a month use; however, the label states that "if re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly." The study therefore included repeated treatments at weekly intervals for a total of four treatments.

D. Experimental design

The dogs were observed daily during study days -14 through -1 (the acclimation period), and twice daily during study days 0 through 37 except on dosing days, when the animals were observed once prior to dosing and 4 times, approximately 1 hour apart, following dosing. These observations included evaluation of the "clinical condition" of the eyes, appetite, feces, respiration, behavior changes, locomotion and musculature, skin, and any signs of vomiting. Physical examinations were conducted prior to the acclimation period and on study days -1 and 37. Body weights were recorded on study days -14, -7, -1, 13, 20, 28, and 37. Food consumption was recorded once daily during the acclimation period and twice daily during the study, except on dosing days, when it was evaluated 5 times; in all cases, a daily summary of food consumption was also made. The amount of food consumed was estimated visually and scored as 1, 2, or 3, indicating, respectively, that greater than or equal to 75%, 25-75%, or less than 25% of the food was consumed.

E. Pathological parameters

Baseline blood samples were collected on study days -7 and -1, and post-treatment blood samples were collected on study days 1, 22, and 37. The report did not mention the venipuncture sites used or whether the animals were fasted overnight prior to blood collection. Additional samples were collected on study days 3 and 8 from one dog (#400) that exhibited elevated alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotrasferase (AST) activities on study day -

1. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)*		
X	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin*
X	Sodium*	X	Glucose*
		X	Total and direct bilirubin*
	ENZYMES	X	Total serum protein*
X	Alkaline phosphatase(ALK)*		(TP)
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)		Albumin/Globulin ratio
X	Serum alanine amino- transferase (also SGPT)*	X	Calcium/phosphorus ratio
X	Serum aspartate amino- transferase(also SGOT)*	X	Blood urea nitrogen/creatinine ratio
	Gamma glutamyl transferase(GGT)	X	Sodium/potassium ratio
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. Statistics

Baseline body weight and clinical pathology values were calculated for each animal by averaging the pre-treatment measurements. Body weight data were analyzed by first comparing the baseline body weights of the two groups by sex with a two-sample t-test. Body weight changes from baseline were calculated for each post-treatment day (study days 13, 20, 28, and 37), and body weight changes were then analyzed by sex with a repeated measure analysis of covariance including terms for Group, Animal (random), Day, and Group*Day interaction with baseline body weight as the covariate. Clinical pathology data were analyzed using a multivariate repeated measures ANOVA,

including terms for Group, Sex, Animal (random), Day, and Group*Day interaction. If the Sex effect was statistically significant at the 0.10 level, the data were analyzed by sex with a multivariate repeated measures ANOVA including terms for Group, Animal (random), Day, and Group*Day interaction. If the Group*Day interaction was statistically significant at the 0.10 level, the data were graphed to investigate the nature of the Group by Day interaction, and the data for each study day were compared with normal ranges.

G. Disposition of animals

Not reported.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

Each 1.0 mL of the product contained 100 mg of imidacloprid and 10 mg of pyriproxyfen. For thirty days' efficacy, the minimum desired efficacious dose for imidacloprid is 10 mg/kg, and the desired minimum efficacious dose for pyriproxyfen is 0.5 mg/kg. In terms of desired minimum efficacious doses in mg/kg, the exaggerated doses used in the study ranged from 5.4X to 13.2X for imidacloprid and 10.8X to 26.4X for pyriproxyfen.

B. Mortality

There were no deaths during the study.

C. Clinical signs

Clinical observations are presented in Table 2. On study day 1, one male in the test substance group vomited some food. On study day 15, one male in the vehicle control group voided a soft stool. On study day 21, several dogs "jumped excessively due to excitement." The study report did not indicate which dogs, the exact number or give any other details other than the fact that three of them (two from the test substance group and one from the vehicle control group) exhibited sore footpads. Following the treatments, the hair coats of dogs from both groups appeared rough, with this appearance lasting for up to 36 hours. No signs of erythema, edema, or alopecia were reported in any of the treated animals.

TABLE 2. Clinical observations of dogs treated with Imidacloprid/Pyriproxyfen Spot-on Formulation.		
Treatment group	**Day**	**Observation**
1. Test Substance	1	Rough hair coat in 2 males and 2 females; vomiting in 1 male
	7	Rough hair in 4 males and 2 females
	14	Rough hair in 2 males and 3 females
	15	Rough hair in 1 male and 2 females
	16	Loose stool in 1 male
	21[a]	Rough hair in 6 males and 6 females, with white powder[b] on 1 male and 1 female; at least 1 male and one female "jumped excessively due to excitement"; sore front foot pad in 1 male; sore rear foot pad in 1 female
2. Vehicle control	1	Rough hair coat in 1 female
	7	Rough hair coat in 3 males and 3 females
	14	Rough hair coat in 3 males and 3 females
	15	Loose stools in 1 male
	21[a]	Rough hair coat in 6 males and 6 females; sore rear foot pad in one male; at least 1 male jumped "excessively due to excitement"

Data taken from text, p. 21and Table 2, p. 27, MRID 45097102.

[a] On page 21 the report stated that on study day 21"several" dogs "jumped excessively due to excitement." Three of those dogs exhibited sore footpads.

[b] The white powder was presumed to be from the drying of the test material.

D. Bodyweight and weight gain

Between study day -1 and study day 13, the mean body weights of all groups (test substance group males, females, and combined and vehicle control group males, females, and combined) decreased. Between study day 13 and study day 37, the mean body weights of all groups increased slightly with each consecutive weighing. The statistical report stated that there was no significant difference between groups in the post-treatment change in body weights.

E. Food consumption

All of the dogs on the study generally consumed greater than or equal to 75% of their food. One female (#397) in the test substance group consumed between 25 and 75% of her food on study days -14, -13, and study days 17-20, and one female (#393) in the vehicle control group consumed between 25 and 75% of her food on study days 20, 30, 31, 33, and 34; both dogs consumed greater than or equal to 75% of their food during

the remainder of the pre-treatment and treatment intervals. The study report did not include the quantities of food the dogs were fed.

F. Hematology

There were no treatment related effects on hematology parameters. There were slight increases in leukocyte and neutrophil counts of one dog in the test substance group (#400, see also, below G. Clinical chemistry) on day -1 as compared with day -7. The day 37 leukocyte and neutrophil counts of three dogs in the vehicle control group were slightly increased, as compared with their baseline pretreatment values. These increases were all very slight, and all values remained within the baseline pre-treatment ranges.

G. Clinical chemistry

There were no treatment related effects on clinical chemistry parameters. One dog (#400) in the test substance group exhibited increased elevated alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotrasferase (AST) activities on study day -1. On study days 1, 3 and 8 ALP and ALT remained elevated; all three parameters were normal on study day 21; and ALP was again slightly elevated on study day 37. These findings were clearly not treatment related, as the initial increases occurred prior to treatment, and these values were excluded from the group means. There was a statistically significant interaction ($p<0.10$) between Group and Day (Group*Day) for creatinine levels in males; however, all creatinine values of all animals were within the normal range throughout the study.

H. Necropsy findings

As no mortalities occurred, necropsies and histopathological examinations were not performed.

IV. DISCUSSION

A. There were no deaths during the study. Following the treatments, the hair coats of dogs from both groups appeared rough, with this appearance lasting for up to 36 hours; however, there were no signs of irritation at the application sites. On study day 1, one male in the test substance group vomited some food, and on study day 15 one male in the vehicle control group voided a soft stool. While these occurrences may be related to treatment, each occurred in only one animal and on only one occasion, and both could be considered as incidental findings or, at most, transient, non-life-threatening signs. On study day 21, several dogs "jumped excessively due to excitement" and two from the test substance group and one from the test vehicle group (subsequently?) had sore footpads. As dogs from both groups exhibited this sign, this sign could not be due to the active ingredients of the product. There were no treatment related effects on body weights, food consumption, or clinical pathology parameters.

B. Deficiencies

Body weights were recorded at weekly intervals, except for week one. It is unfortunate that a dog in the test substance group exhibited abnormal clinical pathology findings on the day prior to treatment which necessitated exclusion of subsequent clinical pathology findings for this dog. Results from tests performed a week earlier had been normal, and presumably the dog had been healthy at physical examinations conducted prior to acclimation and the day before treatment, so this cannot be considered a major deficiency.

It is noted that the proposed products (containing approximately 9% Imidacloprid, but only 0.46% pyriproxyfen, rather than the 0.9% in the formulation as tested) are similar to existing registered products containing 9% Imidacloprid as sole active ingredient. Pyriproxyfen is known to have a low toxicity to mammalian species.

The study is classified as **acceptable** as a companion animal safety study in dogs (OPPTS 870.7200). The lack of any consistent indications of a toxicological response following exposures (a total of 4) to 5X label-specified use applications of the test material indicates that an adequate safety margin exists for this formulation and its proposed use on adult dogs.

DATA EVALUATION REPORT

ADVANTAGE PLUS® 10, 20, 55, AND 100 FOR DOGS
[9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation]

STUDY TYPE: Companion Animal Safety - Puppies (OPPTS 870.7200)
MRID 45097101

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831

Primary Reviewer:
Donna L. Fefee, D.V.M.. Signature: _____
Date: _____

Secondary Reviewers:
Cheryl B. Bast, Ph.D., D.A.B.T. Signature: _____
Date: _____

Robert H. Ross, M.S., Group Leader Signature: _____
Date: _____

Quality Assurance:
Lee Ann Wilson, M.A. Signature: _____
Date: _____

Disclaimer

This review may have been altered subsequent to the contractors signatures above.

Oak Ridge National Laboratory, Managed and Operated by UT-Battelle, LLC, for the U.S. Department of Energy under contract number DE-AC05-00OR22725.

DATA EVALUATION REPORT

ADVANTAGE PLUS® 10, 20, 55, AND 100 FOR DOGS
[9.1% Imidacloprid with 0.9% Pyriproxyfen Spot-on Formulation]

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EPA Reviewer:Byron T. Backus, Ph.D. _____ Date: _____

EPA Work Assignment Manager:John Redden, M.Sc. _____ Date: _____
Registration Division (7505C)

DATA EVALUATION RECORD

STUDY TYPE: Companion Animal Safety/Puppies [OPPTS 870.7200]

EPA I.D. NUMBERS: DP BARCODES: D265771, D265774, D265778, D265784;
MRID NUMBER: 45097101

TEST MATERIAL: Advantage Plus® 10, 20, 55, and 100 for Dogs

STUDY NUMBER: 75119 (150.850)

TESTING FACILITY: Bayer Corporation, Agriculture Division, Animal Health, DeSoto Research Facility, 35040 West 87th Street, Building Number 20, DeSoto, Kansas 66018

SPONSOR: Bayer Corporation, Agriculture Division, Animal Health

TITLE OF REPORT: Evaluation of the general safety of 9.1% (w/w) imidacloprid with 0.9% (w/w) pyriproxyfen spot-on formulation in the target species, seven week old puppies.

AUTHOR: A.S. Abraham

REPORT ISSUED: April 4, 2000

CITATION: Hoskins, J.D. (1990) *Veterinary Pediatrics. Dogs and Cats from Birth to Six Months.* Saunders, Philadelphia.

EXECUTIVE SUMMARY: In a companion animal safety study (MRID 45097101), Advantage Plus® for Dogs (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w) was applied topically at a dose of 2.0 mL/puppy (5X the label specified dose of 0.4 mL/puppy for puppies ≤10 lbs) to a group of 7 male and 7 female beagle puppies, seven weeks of age at the time of first treatment. Individual weights of the puppies in the treatment group ranged from 2.54 to 4.01 lbs (1.15-1.82 kg) on day -1. Controls (7M, 7F; weight range: 2.49-5.03 lbs; 1.13-2.29 kg) were dosed with the vehicle alone at a dose of 2.0 mL/puppy (5.6X the volume of the vehicle present in the specified dose). Both groups were treated on study days 0, 7, 14, and 21. The recommended label dose is once a month. However, the labeling for these

products includes the statement: "If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly."

There were no deaths during the study. Following all treatments, a rough hair coat condition at the application site was noted on 3-14 puppies of both groups, and white powder was occasionally noted at the application sites; however, there were no signs of irritation. One puppy from the test substance group was found to have ocular discharge and "crusty patches" on its ventral abdomen, by the lip and under each eye on study day 36. The puppies completed treatment for coccidiosis on study day -8. During the remainder of acclimation, in the test substance group there were two observations of loose feces with mucous and five observations of diarrhea, with or without mucous or red colored mucous, exhibited by four animals. In the vehicle control group, there were two observations of loose feces with mucous, exhibited by two animals.

During the treatment/observation period, in the vehicle control group, there were seven observations of diarrhea (including one with blood) exhibited by 5 animals, and in the test substance group, there were 2 observations of diarrhea, 4 observations of loose feces with mucous (all four of these observations were made on a single female on day 14 post-application), and one observation of only red mucous. It is noted that there was an increased incidence of loose stools in a considerable number of animals (in both treatment groups) following the second (day 14) treatment. In the test material group, 6/14 puppies had loose stools (one with mucous) at one or more times on day 14 following treatment; only one of these puppies had shown this symptom on day 14 prior to treatment. In the vehicle control group, 5/14 puppies had loose stools after treatment; none had shown this symptom on day 14 before treatment. This was not observed on treatment days 7 and 21, and an examination of the data for day 0 indicates the 3/14 puppies in the test material group showing this symptom after treatment had also shown it before treatment on that day, whereas the 3/14 in the vehicle control group showing this symptom had it only after treatment. Mean leukocyte counts were slightly elevated on study days 1 and 22 for the test substance group and on study day I for the vehicle control group, and the mean neutrophil count for the test substance group was also slightly elevated on study day 1; however, the mean neutrophil count for all puppies on the study was slightly elevated on day -1 (preexposure) as was the leukocyte count. There were no treatment related effects on body weights or food consumption.

The guideline states that animals should be free from infectious diseases which could complicate the interpretation of study results. It is concluded that, while marginal (in the vehicle control group there were 7 observations of diarrhea - one with blood - exhibited by 5 animals, and in the test substance group there were 2 observations of diarrhea in 2 separate females, 4 observations of loose feces with mucous made on a single female on day 14 post-dosing, and one observation of red mucous, exhibited by a male on day 22) these incidences are low enough that we can consider the study not to be compromised. In addition, the puppies had adequate weight gains during the treatment period. Overall, it appears that the puppies were infected when they arrived at the laboratory but were adequately treated. In addition, they may have been under some stress. The Agency recognizes the difficulties inherent in conducting this type of study under these circumstances, particularly when treatment has to be

initiated when the animals are no more than seven weeks old and there are severe scheduling constraints.

It is also noted that this formulation is similar to those of a number of existing registered products, except for the addition of 0.9% pyriproxyfen for efficacy against flea eggs. Pyriproxyfen is known to have extremely low toxicity (both acute and chronic) to mammalian species. In addition, the proposed products which this study is supporting contain 0.46% pyriproxyfen, rather than 0.9%.

Despite the fact that the puppies may not have been entirely free of infection, and despite some deficiencies in the reporting of the data, the study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) in puppies. The lack of any indications of a consistent toxicological response following exposures (a total of 4) to 5X label-specified use applications of the test material indicates that an adequate safety margin exists for this formulation and its proposed use on puppies 7 weeks of age and older.

COMPLIANCE: Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

I. MATERIALS

A. Test material

9.1% (w/w) Imidacloprid with 0.9% (w/w) Pyriproxyfen Spot-on Formulation
(Advantage Plus® 10, 20, 55, and 100 for Dogs)
Description: not provided
Lot No.: 99-901-66
Active Ingredients: Imidacloprid, 9.1% (w/w); Pyriproxyfen, 0.9% (w/w)
Storage Conditions: in the dark in a closed cabinet at room temperature.

B. Administration

Topical (spot-on). From p. 17 of MRID 45097101: "The dose was administered topically on the back. To avoid dose run off, the dose was applied on the top of the back from the shoulder to the base of the tail." This is consistent with proposed labeling.

C. Vehicle

This consisted of the product formulation less the active ingredients.

D. Test animals

Species: Dog
Breed: Beagle
Age and weight at study initiation: 7 weeks; males: 1.13-2.29 kg; females: 1.15-1.77 kg

Source: Marshall Farms USA, Inc., 5800 Lake Bluff Road, North Rose, NY 14516
Housing: Individually in runs of 30.3-36 square feet and greater than 6 feet high.
Diet: Commercial dry and canned food (Hill's Pet Nutrition, Inc. and subsidiaries), once daily
Water: Potable water, *ad libitum*
Environmental conditions: not provided
Acclimation period: 14 days; puppies were vaccinated against canine parvovirus on the second day of the acclimation period and were re-vaccinated on the eleventh day of the acclimation period (study days -13 and -4)

II. STUDY DESIGN

A. In life dates: start: September 14, 1999; end: October 20, 1999

B. Animal assignment/ dosage and administration

Puppies were assigned to the groups in Table I using stratified blocked randomization according to weight. Group 1 received the test substance, and Group 2 received the vehicle without the two active ingredients; puppies in both groups each received a volume of 2.0 mL/puppy at the time of each application. In the case of Group 1, this was equivalent to the 5X use rate volume of the test substance. In the case of Group 2 it was approximately 5.6X the normal use rate of vehicle. Treatments were applied to three or more application sites on the top of the back, from the shoulder to the base of the tail (p. 17 of MRID 450971: "To avoid dose run off, the dose was applied on the top of the back from the shoulder to the base of the tail.") Animals were dosed on Study Days 0, 7, 14, and 21. Dose volumes for treatments on study days 0 and 7 were determined using body weights from study day -1 (all puppies weighed less than 10 lbs). Dose volumes for treatments on study days 14 and 21 were determined using body weights from study day 13 (again, all puppies weighed less than 10 lbs).

TABLE 1. Study design

Group	Number of animals		Dose volume (mL)/ multiple of recommended dose	Number of applications[a]
	Male	Female		
1. Test substance	7	7	2.0 mL/5X	4
2. Vehicle control	7	7	2.0 mL/5.6X	4

Data taken from pp. 12-14, 16-17 MRID 45097101.
[a] Treatment applications were made on Days 0, 7, 14, and 21.

C. Dose selection rationale

The study was conducted as a limit test using 5 times the recommended dose volume. The product, as proposed for registration, would be dosed at the following pre-measured dose volumes: 0.4 mL for dogs or puppies weighing ≤ 10 lbs., 1.0 mL for dogs or puppies weighing 10-20 lbs., 2.5 mL for dogs or puppies weighing 21-55 lbs., and 4.0 mL for dogs or puppies weighing greater than 55 lbs. The puppies in the test substance group all received 2.0 mL dose volumes, since they weighed less than 10 lbs. The vehicle control group received the vehicle at a dose volume equal to 5 times the recommended use volume of the test substance, which was equivalent to 5.6 times the recommended dose volume of the vehicle. The product is intended for once a month use; however, the label states that "if re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly." The study therefore included repeated treatments at weekly intervals for a total of four treatments.

D. Experimental design

The puppies were observed daily during study days -14 through -1 (the acclimation period), and twice daily during study days 0 through 37 except on dosing days, when the animals were observed once prior to dosing and 4 times, approximately 1 hour apart, following dosing. These observations included evaluation of the "clinical condition" of the eyes, appetite, feces, respiration, behavior changes, locomotion and musculature, skin, and any signs of vomiting. Physical examinations were conducted prior to the acclimation period and on study days -1 and 37. Body weights were recorded on study days -14, -7, -1, 13, 28, and 37. Food consumption was recorded once daily during the acclimation period and twice daily during the study, except on dosing days, when it was evaluated 5 times; in all cases, a daily summary of food consumption was also made. The amount of food consumed was estimated visually and scored as 1, 2, or 3, indicating, respectively, that greater than or equal to 75%, 25-75%, or less than 25% of the food was consumed.

E. Pathological parameters

Baseline blood samples were collected on study days -7 and -1, and post-treatment blood samples were collected on study days 1, 22, and 37. The report did not include mention of the particular venipuncture site or sites used or whether the animals were fasted overnight prior to blood collection. To avoid drawing excessively large volumes of blood from puppies as young as 6 weeks of age, coagulation parameters were not measured. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
	Platelet count		Reticulocyte count
	Blood clotting measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)*		
	(Activated partial thromboplastin time)*		
	Erythrocyte morphology		

*Recommended in OPPTS 870.7200 Guidelines.

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
X	Calcium*	X	Albumin*
X	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*		Total Cholesterol
X	Potassium*	X	Globulin*
X	Sodium*	X	Glucose*
		X	Total and direct bilirubin*
	ENZYMES	X	Total serum protein*
X	Alkaline phosphatase(ALK)*		(TP)
	Cholinesterase(ChE)		Triglycerides
	Creatine kinase		Serum protein electrophoresis
	Lactic acid dehydrogenase(LDH)		Albumin/Globulin ratio
X	Serum alanine amino- transferase (also SGPT)*	X	Calcium/phosphorus ratio
X	Serum aspartate amino- transferase(also SGOT)*	X	Blood urea nitrogen/creatinine ratio
	Gamma glutamyl transferase(GGT)	X	Sodium/potassium ratio
	Amylase		
	Glutamate dehydrogenase		

*Recommended in OPPTS 870.7200 Guidelines.

F. Statistics

Baseline body weight and clinical pathology values were calculated for each animal by averaging the pre-treatment measurements. Body weight data were analyzed by first comparing the baseline body weights of the two groups by sex with a two-sample t-test. Body weight changes from baseline were calculated for each post-treatment day (study days 13, 20, 28, and 37), and body weight changes were then analyzed by sex with a repeated measure analysis of covariance including terms for Group, Animal (random), Day, and Group*Day interaction with baseline body weight as the covariate. Clinical pathology data were analyzed using a multivariate repeated measures ANOVA, including terms for Group, Sex, Animal (random), Day, and Group*Day interaction. If the Sex effect was statistically significant at the 0.10 level, the data were analyzed by

sex with a multivariate repeated measures ANOVA including terms for Group, Animal (random), Day, and Group*Day interaction. If the Group*Day interaction was statistically significant at the 0.10 level, the data were graphed to investigate the nature of the Group by Day interaction, and the data for each study day were compared with normal ranges.

G. Disposition of animals

Not reported.

H. Compliance

Signed and dated Quality Assurance, Data Confidentiality, and Good Laboratory Practice Statements were present.

III. RESULTS

A. Exposure levels

Each 2.0 mL of the product contained 200 mg of imidacloprid and 20 mg of pyriproxyfen. For thirty days' efficacy, the minimum desired efficacious dose for imidacloprid is 10 mg/kg, and the desired minimum efficacious dose for pyriproxyfen is 0.5 mg/kg. In terms of desired minimum efficacious doses, the exaggerated doses used in the study ranged from 6.8X to 17.3X for imidacloprid and 13.6X to 34.6X for pyriproxyfen.

B. Mortality

There were no deaths during the study.

C. Clinical signs

Clinical observations are presented in Tables 2 and 3. Both during the acclimation period and the treatment/observation period, there were many incidences of abnormal feces, particularly "loose (soft) feces," but also loose feces containing mucous or diarrhea with or without mucous or a red color (blood?). During acclimation, on study days -12 to -8, all of the animals were treated for coccidiosis with Sulfamethoxazole and Trimethoprim. From study days -7 through -1, in the test substance group there were two observations of loose feces with mucous and five observations of diarrhea (including one with mucous and one with red colored mucous) exhibited by four animals, and one of these animals also had loose feces with mucous on study day 0, prior to treatment. During the same period, in the vehicle control group there were two observations of loose feces with mucous, exhibited by two animals. A considerable number of these occurrences in both groups were on days -12 through -10, possibly correlating with treatment for coccidiosis. There were continued incidences of abnormal

feces during the treatment/observation period. In the test substance group, one animal exhibited loose feces with red mucous prior to treatment on study 0 and diarrhea on day 30, one animal exhibited loose feces with mucous at all four post-treatment observations on study day 14, one animal exhibited red mucous on study day 22, and one animal exhibited diarrhea on study day 29. In the vehicle control group, one animal exhibited diarrhea on study day 7 prior to treatment, one animal exhibited diarrhea with blood prior to treatment on study day 21, one animal exhibited diarrhea on study days 29 and 30, one animal exhibited diarrhea on study day 30, and one animal exhibited diarrhea on study days 33 and 34. One animal in the vehicle control group was diagnosed with coccidiosis on study day 17 and treated with sulfadimethoxine for five days at 25 mg/lb on the first day and 12.5 mg/lb for the next four days. No mention was made of fecal examinations being done, and there were no results from fecal examinations included in the report. It is therefore unclear exactly how the puppy was diagnosed, as his symptoms were less severe than those of some of the other puppies in both groups (2 incidences of "loose feces" during study days 0-16, with no incidences of diarrhea or feces containing mucous). In the test substance group, "loose feces" with no mucous were exhibited by 12/14 puppies during acclimation and 11/14 puppies during treatment/observation on a total of 16 and 71 occasions, respectively, and in the vehicle control group they were exhibited by 9/14 animals during acclimation and 13/14 animals during treatment/observation on a total of 12 and 82 occasions, respectively. In the test substance group 31/71 observations of "loose feces" (without mucous) occurred on treatment days and, of these 31 observations, 22 occurred after treatment, while in the vehicle control group, 26/82 occurred on treatment days, with 20/26 of these from after treatment. There were also infrequent incidences of vomiting: 2 incidences during acclimation in the test substance group, and 2 incidences during treatment/observation in the vehicle control group. One puppy in the test substance group appeared to be favoring its left hind leg following treatment on study day 0. On study day 36 (presumably at physical examination by the veterinarian), one puppy from the test substance group was found to have ocular discharge and "crusty patches" on its ventral abdomen, by the lip and under each eye. Following all treatments, a rough hair coat at the application site was noted on 3-14 puppies of both groups. Following treatment, white powder was noted on the application sites of 3 puppies of the test substance group on day 0, and 1 puppy of the test substance group and 3 puppies of the vehicle control group on day 14. No signs of erythema, edema, or alopecia at the application sites were reported in any of the treated animals.

TABLE 2. Clinical observations of puppies prior to treatment with Imidacloprid/Pyriproxyfen Spot-on Formulation (number of occurrences/number of animals that exhibited the clinical sign)

Observation	Treatment group	
	1. Test substance	2. Vehicle control
Abnormal stools (of any description):	36/13	20/11
loose stools	21/13	16/10
loose stools with mucous	1/1	3/3
loose stools with red-colored mucous	2/2	0
feces comprised of mucous only	1/1	0
diarrhea	5/4	0
diarrhea with mucous	2/2	0
diarrhea with red colored mucous	1/1	0
green diarrhea	0	1/1
mucoid feces	2/2	0
normal stools with mucous	1/1	0
Vomiting	2/2	0
Rapid respiration	2/2	4/4
Slow respiration	1/1	0
Congested or mucopurulent[a]	0	2/2
Total incidences of abnormal feces, excluding those described merely as "loose"	15/7	4/3
Total incidences of abnormal feces, excluding those described merely as "loose," occurring after completion of treatment with Sulfamethoxazole Trimethoprim	6/4	2/2

Data taken from Tables 6A-6G and 7A-7G, pp. 33-40, MRID 45097101.
[a] No further explanation provided in table footnotes or text.

TABLE 3. Clinica) observations of puppies during treatment with Imidacloprid/Pyriproxyfen Spot-on Formulation (number of occurrences/number of animals that exhibited the clinical sign)		
Observation	Treatment group	
	1. Test substance	2. Vehicle control
Abnormal stools (of any description):	70/12	87/13
loose stools	66/11	78/13
loose stools with mucous	1/1	0
red mucous only	1/1	0
diarrhea	2/2	6/4
diarrhea with blood	0	1/1
Vomiting	0	2/2
Ocular discharge and "crusty patches" on ventral abdomen, by the lip and under each eye	1/1	0
Favoring leg following treatment	1/1	0
Total incidences of abnormal feces, excluding those described merely as "loose"	4/4	7/5

Data taken from Tables 6A-6G and 7A-7G, pp. 33-40, MRID 45097101.

D. Body weight and weight gain

Body weight and weight gain data are given in Table 4. The statistical report stated that there was no significant difference between groups in the post-treatment change in body weights from baseline, which was the average of weights from study days -14, -7, and -1. Nine/14 puppies from the test substance group and 6/14 puppies from the vehicle control group lost weight during the first and/or second week of acclimation, but all puppies gained weight during the day -1-13, 13-28, and 28-35 intervals. Mean pre-treatment (days -14 through -1) body weight gains (calculated by reviewer) for all groups (males, females and combined sexes from the test substance and vehicle control groups) were much smaller than post-treatment body weight changes for days -1 to 13 and 13 to 28 (-0.05-0.23 lbs vs. 1.23-2.14 lbs).

TABLE 4. Mean body weights and body weight gains[a] of puppies treated with Imidacloprid/Pyriproxyfen Spot-on Formulation (lbs).

Study day	1. Test substance			2. Vehicle control		
	Combined sexes	Males	Females	Combined sexes	Males	Females
-14	3.24	3.26	3.21	3.07	3.31	2.83
-7	3.25	3.40	3.11	3.15	3.42	2.88
-1	3.25	3.44	3.06	3.27	3.48	3.06
13	4.88	5.30	4.46	4.86	5.43	4.29
28	6.80	7.44	6.17	6.59	7.50	5.68
35	8.30	9.15	7.44	8.09	9.23	6.94
-14 to -7	0.01	0.14	-0.10	0.08	0.11	0.05
-7 to -1	0	0.04	-0.05	0.12	0.06	0.18
-14 to -1	0.01	0.18	-0.15	0.20	0.17	0.23
-1 to 13	1.63	1.86	1.4	1.59	1.95	1.23
13 to 28	1.92	2.14	1.71	1.73	2.07	1.39
28 to 35	1.50	1.71	1.27	1.5	1.73	1.26

Data taken from Table 4A, p. 30, MRID 45097101.
[a]Calculated by contract reviewer.

E. Food consumption

All of the puppies on the study were fed the following amounts of food, once daily: on study days -14 to -13, 3 oz, on study days -12 to 16, 3 oz + 1 tablespoon, on study days 17 to 28, 4.5 oz, and on study days 29 to 35, 6.5 oz. The animals generally either consumed greater than or equal to 75% or 25-75% of their food. During acclimation, 7/14 animals in the test substance group ate less than 25% of their food on one or more days for a total of 14 occurrences, and 4/14 animals in the vehicle control group ate less than 25% of their food on one or more days for a total of 6 occurrences. During treatment/observation, 3/14 animals in the test substance group ate less than 25 % of their food on a total of 4 occasions, and 3/14 animals in the vehicle control group ate less than 25% of their food on a total of 5 occasions. The study author attributed differences in food consumption to feeding the same amount of food to all animals irrespective of differences in body weight and growth rate.

F. Hematology

Statistically significant ($p<0.10$) Group*Day interactions were found for some hematology parameters, including neutrophils, platelets, and leukocytes in the pooled sexes, and MCHC in females. At all time points for both groups, the mean values for platelets fell within the reference range, so intergroup differences were considered biologically insignificant. Mean leukocyte counts were slightly elevated above the reference range (5-17 x $10^3/\mu L$) on study days 1 and 22 for the test substance group (20.16 and 17.61 x $10^3/\mu L$, respectively) and on study day 1 for the vehicle control group (17.1 x $10^3/\mu L$). The mean neutrophil count for the test substance group was also slightly elevated on study day 1 (12.6 x $10^3/\mu L$ vs. a reference range of 3-12 x $10^3/\mu L$). Mean MCHC values for both sexes of both groups were decreased below the reference range at baseline and on days 1, 22, and 35. Without the use of normal reference range values for animals of this age for the laboratory used to test the blood or a complete table of incidences of values outside the reference ranges, this reviewer is unable to definititively state that there were no alterations in any other erythrocyte parameters (hematocrit, hemoglobin, erythrocyte count, MCH, and MCV).

G. Clinical chemistry

Statistically significant ($p<0.10$) Group*Day interactions were found for some blood chemistry parameters, including calcium for the pooled sexes, glucose for males, and chloride for males and females. At all time points for both groups, the mean values for calcium (for the pooled sexes) and glucose (for males) fell within the provided reference ranges, so intergroup differences were considered biologically insignificant. For animals in the test substance group, mean chloride concentrations were decreased on study day one for both sexes and on study day 35 for females. For animals in the vehicle control group, mean chloride concentrations were decreased on study days 1, 22, and 35 in both males and females, and for males only, the baseline concentration was also decreased.

H. Necropsy findings

As there was no mortality, necropsies and histopathological examinations were not performed. The Guidelines for this type of study do not require terminal sacrifice.

IV. DISCUSSION

A. There were no deaths during the study. Following all treatments, a rough hair coat condition at the application site was noted on 3-14 puppies of both groups, and white powder was occasionally noted at the application sites. There were no signs of irritation at the dose sites. One puppy in the test substance group appeared to be favoring its left hind leg following treatment on study day 0, and there were two occurrences of vomiting (once on day 14 following treatment and once on day 17) by puppies in the vehicle control group. These were not considered to be adverse effects. One female

puppy from the test substance group had slight ocular discharge from the right eye and "crusty patches" on its ventral abdomen, by the lip and under each eye on study day 36.

Both during the acclimation period and the treatment/observation period, there were many observations of "loose (soft) feces," and occasional occurrences of loose feces containing mucous or diarrhea with or without mucous or blood. All animals were treated for coccidiosis during acclimation, but continued showing similar signs up to and including the day prior to treatment. In the test substance group, the observation of "loose feces" with no mucous was exhibited a total of 21 times by 13 puppies during acclimation and predosing on day 0, and 63 times by 11 puppies during treatment/observation; Of 31 occurrences on days of treatment (days 0, 7, 14, 21) 9 (including 5 on day 0, including in the total above during acclimation and predosing) occurred before treatment and 22 occurred after treatment. In the vehicle control group, the observation of "loose feces" with no mucous was exhibited 15 times by 9 animals during acclimation and 74 times by 13 animals during treatment/observation. There were 24 occurrences on treatment days (including 4 on day 0) and of these 18 occurred following treatment. However, it is emphasized that what appears to be a significantly increased incidence on days of dosing may be an artifact from the increased number of observations on these days (during this period puppies were being observed twice a day, except for days of dosing, when they were observed pre-dose, and at 4 later times, at 1 hr, 2 hrs, 3 hrs and 4 hrs, post-dosing). As a result, a puppy, such as #431 in group 1 is reported as showing 5 occurrences of loose stools on day 14, once before application of the test material, and 4 times afterwards. If this had occurred on a non-application day, this puppy would have been reported as having 2 occurrences of loose stools (A.M. and P.M.).

Loose feces are not necessarily an abnormal finding among research dogs and puppies, and although at first glance there does appear to potentially be a treatment related pattern to the occurrences of loose feces, there may instead be something else going on. The puppies may have been stressed by the change in routine on treatment days, or perhaps there were more observations of loose feces on those days simply because there were more observation periods. Coprophagia is common in puppies of this age, so some observations of loose feces may have been "missed" on days when the puppies were only observed twice. However, mucoid feces, loose feces with mucous, and diarrhea with or without mucous are all abnormal and should not be seen in healthy animals.

The puppies completed their treatment for coccidiosis on study day -8, but from study day -7 through study day -1, in the test substance group there were two observations of loose feces with mucous and five observations of diarrhea (including one with mucous and one with red colored mucous) exhibited by four animals, and one of these animals also had loose feces with mucous on study day 0, prior to treatment. During the same period in the vehicle control group there were two observations of loose feces with mucous, exhibited by two animals.

Incidences of abnormal feces continued during the treatment/observation period. In the vehicle control group, there were seven observations of diarrhea,(one of these with blood) exhibited by 5 animals (on day 7 predose in one animal, with blood on day 21 predose in one animal, in one animal on days 29 and 30, in another on day 30, and in one animal on days 33 and 34), and in the test substance group, there were 2 observations of diarrhea (one on day 29, and one on day 30, in 2 separate females), 4 observations of loose feces with mucous (all four of these observations were made on a single female on day 14 post-dosing), and one observation of (only?) red mucous, exhibited by a male on day 22. One animal in the vehicle control group was diagnosed with coccidiosis on study day 17 and treated. It is unclear how this diagnosis was made; there was no mention of fecal examinations being done, there were no results from fecal examinations included in the report, and this puppy's symptoms were less severe than those of some of the other puppies in both groups (2 incidences of "loose feces" during study days 0-16, with no incidences of diarrhea or feces containing mucous). If at some point during the study fecal examinations were done which indicated that this nearly asymptomatic puppy had coccidiosis while the others that were showing symptoms did not have coccidiosis, then those results should have been included in the study to aid in interpretation.

It is noted that there was an increased incidence of loose stools in a considerable number of animals (in both treatment groups) following the second (day 14) treatment. In Group 1 puppies 6/14 animals showed loose stools (one with mucous) at one or more times following treatment; only one of these puppies showed loose stools before treatment. In Group 2 there were 5/14 with loose stools after treatment; none had shown this symptom before treatment. This was not observed on days 7 or 14, and an examination of the increased incidence of loose stools on day 0 following treatment (in 3/14 puppies in Group I and 3/14 in Group 2) shows that all 3 puppies in Group I which showed this symptom post-treatment had shown it before treatment; whereas the 3 in Group 2 showed it only following treatment.

There were no clear treatment related effects on food consumption or body weights. However, mean two-week, pre-treatment body weight gains (calculated by the contract reviewer) for all groups (males, females and combined sexes from the test substance and vehicle control groups) were much smaller than post-treatment body weight changes for days -1 to 13 and 13 to 28 (-0.05 to 0.23 lbs vs. 1.23 to 2.14 lbs), and 9/14 puppies from the test substance group and 6/14 puppies from the vehicle control group lost weight during the first and/or second week of acclimation. During the first five months of life, puppies are supposed to gain 1-2 g/day per pound (2-4 g/day/kg) of the expected adult weight (Hoskins, p. 473), and weight losses, especially, ongoing ones, must be scrutinized carefully. Obviously, weight loss or failure to thrive during acclimation does not represent a treatment effect; however, it suggests that the puppies began the study with compromised health and nutritional status, possibly at least partially due to stress associated with weaning, change in surroundings etc.

Mean leukocyte counts were slightly elevated above the reference range on study days 1 and 22 for the test substance group and on study day 1 for the vehicle control group. The mean neutrophil count for the test substance group was also slightly elevated on study day 1. The elevated leukocyte and neutrophil counts could represent either a treatment related effect or be due to coccidiosis or other infection. Unfortunately, clinical pathology testing was not repeated on study day 7, so it is unknown whether there were any further changes in these parameters between study days 1 and 22. Mean MCHC values for both sexes of both groups were decreased below the reference range at baseline and on days 1, 22, and 35. This does not represent a treatment effect but may be consistent with iron deficiency, in which one would also expect to see decreased hematocrit, hemoglobin, erythrocytes, MCH, and MCV. Without the use of normal reference range values for animals of this age for the laboratory used to test the blood or a table of incidences of values outside the reference ranges, this reviewer is unable to definitely state that none of these findings was present. For animals in the test substance group, mean chloride concentrations were decreased on study day one for both sexes and on study day 35 for females. For animals in the vehicle control group, mean chloride concentrations were decreased on study days 1, 22, and 35 in both males and females, and for males only, the baseline concentration was also decreased. This is probably not treatment related. This finding would be most consistent with vomiting, but could also be the result of chloride losses through enteritis.

The study author stated that "the findings of animals with coccidia, sporadic diarrhea or mucus in the feces, and frequent soft stools are considered not to be treatment related as these animals were weaned at five weeks of age and were becoming acclimated to puppy food." It is the opinion of this reviewer that acclimation to puppy food should not still be occurring seven weeks after the diet has changed. The guideline states that animals should be free from infectious diseases which could complicate the interpretation of study results, and, even at the beginning of the study the puppies could not be considered to be entirely free of infectious diseases. However, there was apparently some monitoring of the animals, as one animal in the vehicle control group was determined to have coccidiosis on day 17.

B. Deficiencies

Body weights were recorded on study days -14, -7, -1, 13, 20, 28, and 37, but were not recorded on study day 7. The vehicle control group received the vehicle at a dose volume equal to 5 times the recommended use volume of the test substance, which is equivalent to 5.6 times the usual use volume of the vehicle. The guideline specifies that the vehicle control should be administered at a 5X level and should contain the inert ingredients at the maximum levels that would appear in the 5X formulation; however, since this deviation resulted in the animals receiving slightly higher doses rather than lower doses, it is considered minor.

The guideline specifies that if clinical pathology parameters are "altered" 24 hours post treatment, clinical pathology should be reassessed on day 7. There were alterations in

some clinical pathology parameters (leukocyte and neutrophil counts, and chloride concentrations) on study day 1, but clinical pathology testing did not take place until study day 22.

Due to the questionable health status of the animals during acclimation and up to and including the day prior to the initial treatment, the baseline values for the clinical pathology parameters are not necessarily indicative of normals from this laboratory for animals of this age, making it quite difficult to properly evaluate the clinical pathology data for this study (and the health status of the animals on the study). Normal reference range values for animals of this age for the laboratory used to test the blood or a table of incidences of values outside the ranges should have been included for all clinical pathology parameters instead of only the parameters for which statistically significant Group*Day interactions were found, and in the case of the latter, the data would need to be both pooled and separated by sexes.

The statistical report stated that all neutrophil values for both groups were above the reference range throughout the study (including acclimation), and this agrees with the data in the provided table giving frequencies of values out of normal range for selected clinical pathology parameters (Table III.3); however, the report gave a reference range of 3-12 x $10^3/\mu L$, and all but one of the provided group mean values fell within this range. If all individual values are above the reference range, it is not possible for their means to fall within the range, and, moreover, in examining the individual data, many of the individual values do fall within the reference range. For example, for day 35 in Group I 12/14 of the values fall within the reference range, one is low, and one is high. The report is clearly in error in one or more places.

The statistical report states that statistically significant Group*Day interactions were found for MCHC in males (p. 87); however, the accompanying table (Table III.1, p. 87) gives the means and standard deviations for females, and the figure (Figure III.1) is labeled "Mean Corpuscular Hemoglobin Conc Across Study Days by Treatment Group Males" but is a graphic representation of the data for females.

The guideline states that animals should be free from infectious diseases which could complicate the interpretation of study results. It is concluded that, while marginal (in the vehicle control group there were 7 observations of diarrhea - one with blood - exhibited by 5 animals, and in the test substance group, there were 2 observations of diarrhea in 2 separate females, 4 observations of loose feces with mucous made on a single female on day 14 post-dosing, and one observation of red mucous, exhibited by a male on day 22) these incidences are low enough that we can consider the study not to be compromised. In addition, the puppies had adequate weight gains during the treatment period. Overall, it appears that the puppies were infected when they arrived at the laboratory but were adequately treated. In addition, they may have been under some stress. The Agency recognizes the difficulties inherent in conducting this type of study under these circumstances, particularly when treatment has to be initiated when the animals are no more than seven weeks old and there are severe scheduling constraints.

It is also noted that this formulation is similar to a number of existing registered products, except for the addition of 0.9% pyriproxyfen for efficacy against flea eggs. Pyriproxyfen is known to have extremely low toxicity (both acute and chronic) to mammalian species. It is also noted that the proposed products will contain 0.46% pyriproxyfen, rather than the 0.9% that was in the formulation as tested.

Despite the fact that the puppies may not have been entirely free of infection, and despite some deficiencies in the reporting of the data, the study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) in puppies. The lack of any indications of a consistent toxicological response following exposures (a total of 4) to 5X label-specified use applications of the test material indicates that an adequate safety margin exists for this formulation and its proposed use on puppies 7 weeks of age and older.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D265774
2. **PC CODES:** 129099 Imidacloprid; 129032 Pyriproxyfen
3. **CURRENT DATE:** September 8, 2000
4. **TEST MATERIAL:** 9.1% (w/w) Imidacloprid with 0.9% (w/w) Pyriproxyfen Spot-On Formulation

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Companion anima(safety/adult dog (beagle)/Bayer Corporation, Agriculture Division, Animal Health/7512 t/APR-04-2000	45097 t02	Formulation was applied topica(ly to a group of 6M and 6F dogs. Dose vo(umes were 5.0 mL for dogs t t-20.4 lbs and at t2.5 mL for dogs 20.5-55 lbs (5X label specified application rate) on study days 0, 7, t4 and 21. Controls (6M, 6F) were treated at the same dosage volumes with vehicle (formulation less active ingredients) on these days. Most prominent clinical sign was a rough appearance of hair at application sites fo(lowing treatment and up to 36 hrs later; however, there were no signs of derma(irritation. Lack of any consistent indications of a toxicological response following exposures (total of 4) to 5X label-specified use applications of the test substance indicates that an adequate safety margin exists for this formu(ation and its proposed use on adu(t dogs. (t is also noted that this formulation is similar to some existing registered products, except for the addition of 0.9% pyriproxyfen, which has a relatively (ow mammafian toxicity.	N.A.	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Companion animal safety/puppy (beagle)/Bayer Corporation, Agriculture Division, Animal Health/75119/APR-04-2000	45097101	Formulation was applied topically to a group of 7M and 7F puppies which were 7 weeks of age at the time of first application. Dose volumes were 2.0 mL/puppy (5X the label specified dose of 0.4 mL for puppies ≤ 10 lbs) on study days 0, 7, 14 and 21. Controls (7M, 7F) were treated at the same dosage volume with vehicle (formulation less active ingredients) on these days. Following all treatments, a rough hair coat condition at the application site was noted for 3-14 puppies of both groups, and white powder was occasionally noted at the application sites; however, there were no signs of irritation. During the treatment/observation period in the vehicle-control group there were 7 observations of diarrhea (one with blood) in 5 animals, and in the test group there were 2 observations of diarrhea, 4 observations of loose feces with mucous (all 4 obsevations were from a single female on day 14 post-application), and one observation of only red mucous. There was an increased incidence of loose stools in a considerable number of animals (both treatment groups) on day 14 post-application, but not on days 0, 7 or 21. Lack of any consistent indications of a toxicological response following exposures (total of 4) to 5X label-specified use applications of the test substance indicates that an adequate safety margin exists for this formulation and its proposed use in puppies 7 weeks and older. It is also noted that this formulation is similar to some existing registered products, except for the addition of 0.9% pyriproxyfen, which has a relatively low mammalian toxicity.	N.A.	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SEP - 7 2000

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Applications for New Advantage Products
Tox and Animal Safety Studies
Reg Nos. For Tox Studies: 11556-REO, REI, RET, REL, REA
Reg NO. For ASS: 11556-11556-RGN
Your submission date, April 7, 2000

Dear Mr. McNamara:

Just a note to let you know that we are coming to a close with reviewing your six new product applications for Advantage. Enclosed is a copy of one completed animal safety study review and five tox study reviews. To complete the reviews, five animal safety study reviews are need. Upon completion, I will notify you as to when you can commence with label changes needed to satisfy registration of your products. If there are questions, call me 703 305-5409.

Sincerely,

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

August 30, 2000

MEMORANDUM

EPA File Symbol: 11556-REI Advantage® Plus 10 for Dogs
DP Barcode: D265773
Case No: 068809
PC Codes: 129099 Imidacloprid; 129032 Pyriproxyfen

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505C)

Byron T. Backus 8/30/2000

To: Helene Daniel/Tina Levine, PM 04
Insecticide-Rodenticide Branch
Registration Division (7505C)

Registrant: Bayer Corp.

ACTION REQUESTED: Review a six-pack of acute toxicity studies. These studies are being used to support the proposed registrations of 6 products, which will be used to control fleas on domestic animals. The MRID numbers of these studies are 45096904 through 45096909.

COMMENTS AND RECOMMENDATIONS: The six acute toxicity studies have all been classified as acceptable, and the proposed product, EPA File Symbol 11556-REI

(ADVANTAGE PLUS 10 FOR DOGS) has the following acute toxicity profile:

Acute Oral LD50	III	Acceptable
Acute Dermal LD50	IV	Acceptable
Acute Inhalation LC50	IV	Acceptable
Primary Eye Irritation	III	Acceptable
Primary Dermal Irritation	IV	Acceptable
Dermal Sensitization	No	Acceptable

These studies were conducted on a formulation containing 9.1% Imidacloprid and 0.9% Pyriproxyfen. The proposed product has a label declaration of 9.1% Imidacloprid and 0.46% Pyriproxyfen, with 90.44% inert ingredients.

It is emphasized that there are additional studies (companion animal safety studies) which have been submitted in support of the registration of this product. These companion animal safety studies should be reviewed and classified as acceptable before this product is registered.

Since the Oral LD_{50} value is below 1500 mg/kg, and this product has residential uses, then it will require Child Resistant Packaging (CRP).

The following is the precautionary labeling for this product, based on the acute toxicity profile given above, and as obtained from the Label Review System:

Date: 08/30/00 LABEL REVIEW SYSTEM

ID #: 011556-00128 Advantage Plus 10 for Dogs

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything by mouth to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN:

Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician." The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100, formerly §81-1))

Product Manager: 04
MRID No.: 45096904

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: September 30, 1999
Study No.: 99-A12-DZ

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (Crl:WI(Glx/BRL/Han)IGS BR
Age: Young adult (Males: 9-10 weeks; Females: approximately 12 weeks)
Weight: Males: 194-242 g; Females: 159-207 g
Source: Charles River Laboratories, Raleigh, NC

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: = 1283 (95% C.L: 680-1678) mg/kg
   Females: = 1000 (95% C.L: not calculable) mg/kg
   Combined: = not reported
2. **The estimated LD_{50} is** = t000 mg/kg
3. **Tox. Category:** III **Classification:** Acceptable

Procedure (including deviations from 870.1100): "Groups of six male and six female rats were treated by gavage at varying concentrations of Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in vehicle (deionized water/PEG 200 1:1 v/v)." Groups of male rats were treated at nominal doses of 1000, 1500 and 2000 mg/kg while groups of female rats were treated at nominal doses of 500, 1000 and 2000 mg/kg... "Six male and six female rats were dosed with vehicle and served as concurrent control groups."

Results:

Dosage (mg/kg)[a]	Number of Deaths/Number Tested		
	Males	Females	Combined
0	0/6	0/6	0/t2
500	-	0/6	-
1000	1/6	3/6	4/12
1500	5/6	-	-
2000	5/6	6/6	11/12

[a]Average actual doses were 0, 1038, 1542 and 2145 mg/kg for males and 0, 614, 1027 and 2071 mg/kg for females.

Observations: There were no clinical signs of toxicity in the females dosed at 500 mg/kg. Symptoms at 1000 mg/kg included: brown nasal staining, brown oral staining, decreased activity, tremors and (females only) urine staining. Symptoms at 1500 and 2000 mg/kg included ataxia, decreased activity and tremors. Mortalities, when they occurred, were on days 0 to 2.

Gross Necropsy: "The following compound-related gross observations were observed at necropsy only in animals that were found dead: salivation and nasal discharge in males and females, red discolored lungs and urine in males. There were no gross observations noted in females from the 500 mg/kg dose group or in males from the 1000 mg/kg dose group. Also, there were no gross observations noted in any surviving, treated male or female rats or in control male or female rats.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200, formerly §81-2)

Product Manager: 04
MRID No.: 45096905

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: September 30, 1999
Study No.: 99-A22-EA

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W. and Berry, L.A.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (Crl:WI(Glx/BRL/Han)IGS BR
Age: Young adult (Males: approximately 9 weeks; Females: approximately 12 weeks)
Weight: Males: 192-245 g; Females: 174-210 g
Source: Charles River Laboratories, Raleigh, NC

Dermal LD_{50} Testing:

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: > 5000 mg/kg (0/6 died)
   Females: > 5000 mg/kg (1/6 died)
   Combined: > 5000 mg/kg (1/12 died)
2. **The estimated LD_{50} is** > 5000 mg/kg
3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (including deviations from 870.1200): "Hair from the dorsal and lateral areas of the trunk...was removedon the day prior to dose application... Groups of six males and six females each received a single dose of either 0 (deionized water) mg/kg or 5000 mg of the undiluted test substance/kg of body weight. For the animals treated with the Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On, measured aliquots of the undiluted test substance were applied uniformly... directly to the shaved area of the animal's back and then a plastic-backed, two-ply gauze patch... was used to cover the dosed area... The gauze patch was held in place with hypoallergenic tape. The animal was then wrapped with an elastic bandage, which was also secured with tape. After a minimum of 24 hours, the bandages and patch were removed and the dose site was wiped using paper towels dampened with tap water to remove as much test substance residue as feasible without inducing skin damage..."

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
0	0/6	0/6	0/12
5000	0/6	1/6	1/12

Observations: "One female from the 5000 mg/kg dose group...was found dead on post-

treatment day 2... Clinical signs of red lacrimal staining, nasal staining, fecal and urine staining in males and females are considered to be unrelated to treatment with the test substance since they occurred at a comparable incidence in control and treated animals. These signs as well as ungroomed appearance in two control males are ascribed to the manipulation and subsequent wrapping of the animal that is associated with dermal exposure and/or the use of Elizabethan collars... Compound-related clinical signs of decreased activity, labored breathing, and rales were observed in one treated female which died on post-treatment Day 2."

Gross Necropsy: "There were no compound-related gross observations noted at necropsy for the males or females that survived until terminal sacrifice. Observations of nasal discharge and urine stained ventrum were observed in one treated female that was found dead on post-treatment Day 2 and were considered compound-related."

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (870.1300, formerly §81-3)

Product Manager: 04
MRID No.: 45096906

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 25, 1999
Study No.: 99-A42-EB

Testing Facility: Bayer Corporation, Agriculture Division Toxicology, Stilwell, Kansas
Author: Sturdivant, D.W.

Quality Assurance (40 CFR §160.12): Included (p. 6-7)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41

Species: Rat; Wistar Hannover (Crl:WI(Glx/BRL/Han)IGS BR
Age: Young adult (Males: approximately 9 weeks; Females: approximately 12 weeks)
Weight: Males: 207-270 g; Females: 192-217 g

Source: Charles River Laboratories, Raleigh, NC

Conclusion:

1. **LC_{50} (mg/L):**
   Males: > 2.50 mg/L (0/6 died)
   Females: > 2.50 mg/L (0/6 died)
   Combined: > 2.50 mg/L (0/12 died)
2. **The estimated LC_{50} is** > 4.21 mg/L
3. **Tox. Category:** IV **Classification:** Acceptable

Procedure (including deviations from 8700.13): Exposure was for four hours, and was nose-only. "The test substance was generated as a liquid aerosol with a respirable particle size distribution."

Exposure Concentration ± S.D. mg/L (Analytically Determined)	Number of Deaths/Number Tested		
	Males	Females	Combined
0[a]	0/6	0/6	0/12
2.50 ± 1.10	0/6	0/6	0/12

[a]A group of 6 male and 6 female rats was "shamp-exposed to conditioned air via the nose-only route for a single four-hour period."

Clinical Observations: There were no deaths. "Clinical signs observed during this study were red perigenital staining, fecal staining and ungroomed appearance and were observed only on Day 0. Although the incidence of these signs was slightly higher in animals exposed to the test substance than air-control animals, they are considered a result of restraint during the exposure period and are not considered compound-related."

Gross Necropsy Findings: "No gross observations were observed at necropsy during this study."

Chamber Atmosphere			
Analytical Concentration	**Nominal Concentration**	**MMAD (µm)**	**GSD**
2.50 mg/L	3.20	2.61	3.02

59% of the particle mass was less than 4 µm, and 26% was less than 1 µm. These percentages are the means of 5 samples.

Other Information:

Chamber Environment [a]	
Chamber Volume	27 L
Airflow (exhaust flow rate)	28 LPM
Mean Chamber Temperature	23.5 °C
Relative Humidity	81%[a]

[a]The high relative humidity is attributed to a high percentage of water contained in the test substance formulation.

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400, previously §81-4)

Product Manager: 04
MRID No.: 45096907
Sponsor Study No.: 99C-I35-FG

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: November 19, 1999
Study No.: Covance 90801932

Testing Facility: Covance Laboratories Inc., Madison, WI 53704
Author: Glaza, S.M.

Quality Assurance (40 CFR §160.12): included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-901-73
Dosage: 0.1 mL
Species: Rabbits; Albino, Hra(NZW) SPF strain
Age: approximately 16 weeks of age
Weight: 2.57-2.707 kg
Source: Covance Research Products Inc., Kalamazoo, MI
Conclusion:

1. **Toxicity Category:** III
2. **Classification:** Acceptable

Procedure (including deviations from 870.2400): Three rabbits were used. "The test substance was administered as received... Initially one animal was treated and the results evaluated. Based on the irritation observed, the other two animals were then treated in the same manner. Each rabbit received 0.1 mL of the undiluted test substance placed into the everted lower lid of the right eye... The upper and lower lids were gently held together for 1 second to prevent loss of material and then released. The eyes of the rabbits remained unflushed immediately after treatment."

Observations	Number "positive"/number tested						
	Hours				Days		
	1	24	48	72	4	7	14
	Unwashed eyes						
Corneal Opacity	3/3	3/3	3/3	3/3	1/3	0/3	0/3
Iritis	3/3	3/3	3/3	2/3	1/3	0/3	0/3
Conjunctivae:							
Redness[1]	3/3	3/3	3/3	3/3	2/3	0/3	0/3
Chemosis[1]	3/3	3/3	3/3	2/3	0/3	0/3	0/3
Discharge[1]	3/3	2/3	3/3	2/3	0/3	0/3	0/3

[1]Score of 2 or greater considered as a positive effect.

"Sodium fluorescein examinations were used to aid in revealing possible corneal injury at the observations conducted at 24, 48, 72, and 96 hours and Day 7 or until a negative response for

that animal was obtained."

Summary: "All 3 animals showed excessive pawing at the treated eye after test substance installation, and one animal vocalized following test substance instillation. All eyes had cleared by day 7 except for grade "1" conjunctival redness (not considered a positive response) in all 3 eyes; at day 14 all scores were zero.

DATA REVIEW FOR DERMAL IRRITATION TESTING (870.2500, previously §81-5)

Product Manager: 04
MRID No.: 45096908
Sponsor Study No.: 99C-I25-DL

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 6, 1999
Study No.: Covance 90503024

Testing Facility: Covance Laboratories Inc., Madison, WI 53704
Author: Glaza, S.M.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-625-41

Dosage: 0.5 mL
Species: Rabbit; albino, HRA:(NZW)SPF
Age: approximately 15 weeks old
Weight: 2.308-2.554 g
Source: Covance Research Products Inc., Kalamazoo, MI

Conclusion:

1. **Toxicity Category:** IV
2. **Classification:** Acceptable

Procedure (including deviations from 870.2500): Three rabbits were used. "The undiluted test substance was applied to the intact skin site on each animal's back (approximate exposure area 6.25 cm^2) in the amount of 0.5 mL. Each area of application was covered with an 8-ply 2.5-cm x 2.5-cm gauze patch secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape to provide a semiocclusive dressing... At the end of the 4-hour exposure period, the patches were removed and the test sites were washed using liquid Ivory® soap mixed with water, rinsed with water, and dried with disposable paper towels. Any residual test substance was removed from the test sites as thoroughly as possible without irritating the skin."

Results: All scores (4, 24, 48 and 72 hrs) for erythema and edema were zero. The PII = 0.0

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600, formerly §81-6)

Product Manager: 04
MRID No.: 45096909
Sponsor Study No.: 99C-I24-DN

Reviewer: Byron T. Backus, Ph.D.
Study Completion Date: October 6, 1999
Study No.: Covance 90503026

Testing Facility: FMC Corporation Toxicology Laboratory, Princeton, NJ 08543
Author: Freeman, C.

Quality Assurance (40 CFR §160.12): Included (p. 4)

Test Material: Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On; a clear, light-yellow liquid, Lot No. 99-625-41

Positive Control Material: alpha-hexylcinnamaldehyde
Species: Guinea pigs, albino; Crl:(HA)BR
Age: Young adult; 5-7 weeks of age at initiation of dosing
Weight: 375-468 g
Source: Charles River Laboratories, Inc., Kingston, NY
Method: modified Buehler

Conclusion:

1. **There is no indication that this product is a dermal sensitizer.**
2. **Classification:** Acceptable

Procedure (including deviations from 870.2600): A group of 20 guinea pigs (10M and 10F) were exposed to the test material during both induction and challenge, while an additional group of 10 (5M and 5F) served as the naive controls, and were exposed at challenge only. In the induction phase, "the undiluted test substance was applied to each animal in the test group by placing 0.4 mL on an adhesive patch (Hill Top Chamber®, 25-mm diameter) and placing the patch on the induction site along the dorsal anterior left quadrant. The patch was covered with dental dam and overwrapped with Elastoplast® tape. The dressing remained in place for a period of 6 hours after which it was removed. Any residual test substance was then removed from the application site using water and disposable paper towels.

The laboratory test system was validated by using alpha-hexylcinnamaldehyde as a positive control within the previous six months (positive control study completed August 4, 1999; study with Imidacloprid (9.1%)/Pyriproxygen (0.9%) Spot On was completed on October 6, 1999).

In the induction phase, 0.4 mL aliquots of the undiluted test material were applied using Hilltop Chambers, with 6-hour exposure periods. The animals in the test group received one application per week for a total of three applications. Challenge was 2 weeks after the last induction application with the same amount of test material at a previously unexposed site; in addition to the 20 animals which had been previously exposed, a group of 10 naive animals was similarly treated.

Results: There was no irritation (all scores were zero) at 24 hours following each induction application. At challenge, 2/20 previously induced animals, as well as 1/10 naive controls, showed a score of 0.5 at 24 hours. All animals (previously induced and naive control) scored 0 at 48 and 72 hrs following challenge treatment.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D265773
2. **PC CODE:** 129099 Imidacloprid; 129032 Pyriproxyfen
3. **CURRENT DATE:** August 30, 2000
4. **TEST MATERIAL:** Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On; a clear yellow to light brown liquid, Lot No. 99-625-41 (used for all studies except primary eye irritation); Lot No. 99-901-73 (used for primary eye irritation)

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/Bayer Corp. Toxicology/99-A12-DZ/SEP-30-1999	45096904	LD_{50} (M) = 1283 (95% C.L. 680-1678) mg/kg; LD_{50} (F) = 1000 (95% C.L. not calculable) mg/kg	III	A
Acute dermal toxicity/rat/Bayer Corp. Toxicology/99-A22-EA/SEP-30-1999	45096905	LD_{50} > 5000 mg/kg (0/6M, 1/6F females died following dosage at this level)	IV	A
Acute inhalation toxicity/rat/Bayer Corp. Toxicology /99A42-EB/OCT-25-1999	45096906	LC_{50} > 2.50 mg/L (males, females, combined). No mortalities following 4-hr exposure to this concentration.	IV	A
Primary eye irritation/rabbit/Covance Laboratories Inc./Covance 90801932/NOV-t9-1999	45096907	Three eyes tested: All showed corneal opacity through 72 hrs. All eyes had cleared by day 7 except for grade "1" conjunctival redness (not considered a positive response) in all 3 eyes; at day 14 all scores were zero.	III	A
Primary dermal irritation/rabbit/ Covance Laboratories Inc./Covance 90503024/OCT-6-1999	45096908	All scores zero at 1, 24, 48 and 72 hrs. PII=0.00.	IV	A
Dermal sensitization/guinea pig/ Covance Laboratories Inc./Covance 90503026/OCT-6-1999	45096909	Not a sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 16 2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Mr. F. Terry McNamara
Bayer Corporation
Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

Subject: Application for New Dog Products

Advantage Plus 10 for Dogs	Reg No. 11556-REI
Advantage Plus 20 for Dogs	Reg No. 11556-REL
Advantage Plus 55 for Dogs	Reg. No. 11556-RET
Advantage Plus 100 for Dogs	Reg. No. 11556-RGN

Your submission date, April 7, 2000

Dear Mr. McNamara:

The labeling referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide, and Rodenticide Act as amended is unacceptable for the reason listed below:

The product chemistry reveiw for the above products have been completed. The chemist has determined that your submitted labels and confidential statements of formula contains a number of deficiencies that need to be addressed. However, the animal safety study reviews and the tox reviews are yet to be completed. Please hold off making any corrections to the labels, until you receive the entire package. Enclosed are copies of the product chemistry reviews to help guide you in correcting the labels and the confidential statements of formula. If there are questions concerning these reviews, call me at 703 305-5409.

Sincerely,

/s/

Dani Daniel
Insecticide-Rodenticide Branch
Registration Division 7505C

Enclosure:

Product ingredient source information may be entitled to confidential treatment

DATE: 2/JUNE/2000

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.:D265772 REG./File Symbol No.:11556-REI
PRODUCT NAME: Advantage Plus 10 for Dogs
COMPANY: Bayer Corporation

FROM: Linda L. Kutney, Chemist
Product Chemistry Team
Technical Review Branch (TRB)/RD (7505C)

TO: Tina Levine/Dani Daniel, PM #4
Insecticide Branch/RD(7505C)

INTRODUCTION

The Bayer Corporation has applied for registration of six new insecticides intended to kill fleas on different sizes of cats and dogs. All six of these products contain identical confidential statements of formula, CSFs (dated 4-7-00) and separate proposed labels, also dated 4-7-00.

This review covers one of the six insecticides, the subject product named, Advantage Plus 10 for Dogs, Once-A-Month Topical Flea Treatment for Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under, Reg. No. 11556-REI, which Bayer submitted a me-too application, based on their product Advantage 10, EPA Reg. No. #11556-117.

The subject Advantage Plus product differs from the older Advantage product in that it includes 0.46% of an insect growth regulator pyriproxyfen, added to help control flea eggs, and contains an additional inert. The subject product reportedly controls larval and adult fleas, as well as flea eggs, and is to be applied to the back of the neck or shoulders of the dog.

Bayer submitted the CSF and proposed label for the subject product and the studies entitled, "Imidacloprid/pyriproxyfen Spotton Formulation (containing 5% water) Product Chemistry," dated 11-22-99, MRID 450969-03, "Product Chemistry of (10%w/v, 9.1% w/w) Imidacloprid & (0.5% w/v, 0.46% w/w) Pyriproxyfen TopicalSolution -Product Identity, Composition and Analysis," dated 12-16-99, MRID 450969-02 and "Validation of Bayer Animal Health Test Method -TMC-14.02 for the Determination of Imidacloprid and Pyriproxyfen in the (10%w/v, 9.1% w/w) Imidacloprid & (0.5% w/v, 0.46% w/w) Pyriproxyfen Topical Solution Formulation by HPLC," dated 1-26-00, MRID 450969-01.

The subject product is a liquid containing two active ingredients, a.i.'s, 9.10% imidacloprid [redacted]

Product ingredient source information may be entitled to confidential treatment

and 0.46% pyriproxyfen [redacted] and 90.44% inert ingredients.

FINDINGS

TRB has reviewed this submission and reports the following findings:

- All of the inert ingredients are cleared for use in formulated pesticides.
- The CSF exceeds the limits for nominal, upper and lower limits of the a.i.'s (40CFR 158.175) and the nominal concentrations on the draft label and CSF are different.
- The inerts listed on the CSF do not include the name and address of the suppliers.
- The draft label contains appropriate storage and disposal instructions.
- The enforcement method (40CFR 158.180) is labeled "Confidential Business Information."
- Data requirements for product identity and composition (40CFR 158.155), production process (40CFR 158.162), formulation process(40CFR 158.165), impurities (40CFR 158.1670), description of materials used in production (40CFR 158.160), preliminary analysis (40CFR 158.170) and submittal of samples (40CFR 158.190) are satisfied.
- Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 are satisfied with the exception of explodability (830-6315), Storage Stability of the Product (830-6317), and miscibility (830-6319).
- The subject product contains an a.i. and an impurity which is not present in the product Bayer wishes to "me-too," and the nominal concentrations and certified limits of the subject product and the product to be "me-too-ed" are different.
- The pH and density of the subject product and the product the me-too application is based on are different.

CONCLUSION

TRB has reviewed this submission and concludes the following:

- Because the nominal concentrations of a.i.'s on the CSF are not identical to the label concentrations, the Registrant should resubmit the CSF and label and ensure that the concentrations of the a.i.'s are correct and identical.

- The name and address of the suppliers of inerts should be included on a revised CSF.

- The enforcement analytical method (40CFR 158.180) will be satisfactory, providing the Registrant submits a new copy not labeled "Confidential Business Information." This is a 3-97 FIFRA requirement (Section 10 (d)(1))needed for enforcement purposes, etc.

- Group B Product chemistry requirements listed in Series 830 Guidelines under 40CFR 158.190 explodability (830-6315), Storage Stability of the Product (830-6317), miscibility (830-6319) and dielectric breakdown voltage (830-6321) have not been fulfilled and should be submitted.

- The subject product, Reg. No. 11556-REI, is not substantially similar to EPA's Reg. No. 11556-117, from a product chemistry point of view, because it contains an additional a.i. and inert ingredient, and because the nominal and certified limits of the components are not substantially similar (see the Confidential Appendix for details).

1. Reviewer: Linda L. Kutney

2. Company: Bayer Corporation

3. Type of Submission: Registration [X] Reregistration [ ]
New [X] Resubmission [ ] Amendment [ ] "ME-TOO" [X]
Alternate Formulation [ ] Experimental Use Permit [ ]
Other (Specify)

4. If "Me-TOO" Registration, this product is [ ] is not [X[
similar or substantially similar to EPA's Reg. No.:
11556-117
If not, comment in Confidential Appendix on the significant differences between the registered and the new source.

CONFIDENTIAL STATEMENT OF FORMULA

5. Type of formulation and the sources of active ingredients:
• Non-integrated formulation system.....[X]
• Are all technical grade active ingredients used registered? • yes [X] • no [ ], If no, specify
• Integrated formulation system.....[ ]

6. Clearance of intentionally added ingredients in the formulation for the intended use (indicate in the Confidential Appendix those that are not cleared; the PC Codes should be provided by the chemist on the CSF for those that are cleared):

6(a) Formulation intended for food use under 40CFR§180.1001:
• yes [ ] • no [X] • Some are cleared, others are not [ ]
Cleared under list: • c[ ] • d[ ] • e [ ]

Are there any limitations for use as an inert under 40CFR§180.1001?

• yes [ ] • no [X], If yes, specify

6(b) Formulation intended for non-food use:
• yes [X] • no [ ] • Some are cleared, others are not [ ]

6(c) Clearance by the FDA of certain formulations under 21CFR§170 to 199,e.g.,(a) indirect food additives, such as food contact surface sanitizers; adhesives, coatings, paper and paperboard products that may contact food in packaging or holding; & (b) substances generally recognized as safe,GRAS
• yes [ ] • no [X] • Some are cleared, others not [ ]
If yes, the entire formulation is cleared under 21CFR§

Product ingredient source information may be entitled to confidential treatment

7. The density, pH, and flammability values given on the CSF are identical with those of GRN 830.7300(density), 830.7000(pH), and 830.6315(Flammability), respectively:
• yes [X] • no [ ]

8. The nominal concentrations (NC) of the active ingredients and the upper and lower certified limits (UCL & LCL) are as follows:

Active ingredient(s)	REG-NO	% by weight NC	UCL	LCL
Imidacloprid	[redacted]			
Pyriproxyfen				

9. The calculated NCs, based on the pure active ingredients (PAI), are identical to those on the label:
• yes [ ] • no [X]
Not acceptable for imidacloprid and Pyriproxyfen-as required in PR Notice 91-2

10. The certified limits are within the standard limits as per 40CFR§158.175 or are adequately explained if different:
• yes [ ] • no [X]

PRODUCT LABEL

11. The chemical names of the active ingredients on the label are identical to those on the CSF: • yes [X] • no [ ]

12. The appropriate physical and chemical hazards statement regarding flammability or explosive characteristics of the product are given on the label:
• yes [ ] • no [ ] • not applicable [X]

13. The storage and disposal instructions for the pesticide and container are in compliance with PR Notice 84-1 for household use products or PR Notice 83-3 for all other uses:
• yes [X] • no [ ]

PRODUCT CHEMISTRY DATA (SERIES 830 Subgroup A & Subgroup B)

14. Chemical IDs/Manufacture/ Analytical Information New Guideline:830.--	Data Required Fulfilled	MRID No.
1550.(61-1)Chemical Identity(CSF)	Y	450969-02
1600.(61-2a) Beginning Materials 1620.(61-2b) Formulation Process	Y	450969-02
1670.(61-3) Discussion of Impurities	Y	450969-02
1700.(62-1) Preliminary Analysis	Y	450969-02
1750.(62-2) Certified Limits(CSF)	N	450969-02
1800.(62-3)Enforcmnt. of Anal.Method	Y	450969-01

15. Physical/Chemical Properties New Guideline No. 830.---	Data Required Fulfilled	Value or Qualitat. Descrip.	MRID No.
6303.(63-3)Physical State	Y	Liquid	450969-03
7300.(63-7)Density/Bulk Density	Y	1.092 lbs/gal	450969-03
7000.(63-12) pH	NA	6.02	450969-03
6314.(63-14)Oxid/Red Action	Y	No ox. Or red. Action	450969-03
6315.(63-15a)Flamm.-Flsh Pt.	Y	above 100.2°C	450969-03
6315.(63-15b) Flame Exten.	NA		--
6316.(63-16)Explodability	N	--	--
6317.(63-17)Storage Stability.	N	--	--
7100.(63-18)Viscosity	Y	5.13 cSt	450969-03

6319.(63-19) Miscibility	N	--	--
6320.(63-20) Corrosion Characteristics	Y	Non-corrosive as packaged, tested for about 30 days	450969-03
6321.(63-21) Dielectric Breakdown Voltage	N	---	--

Explanations: Y = The Requirements Were Fulfilled; N = The Requirements Were Not Fulfilled; NA = Not Applicable; G = Data Gap; U = Requires Upgrading; I = Incomplete or In Progress; W = Waived.

Inert ingredient information may be entitled to confidential treatment

CONFIDENTIAL APPENDIX

SUBJECT: PRODUCT CHEMISTRY REVIEW OF MP [ ] EP [X]
DP BARCODE No.: D265772 REG./File Symbol No.: 11556-REI
PRODUCT NAME: Advantage Plus 10 for Dogs
COMPANY: Bayer Corporation

- The CSF for the subject product, contains a nominal concentration of imidacloprid of 8.9% and of pyriproxyfen of 0.45%, not 9.10% and 0.46%, respectively, as stated on the proposed label. The registrant should resubmit the CSF and proposed label and ensure that these percentages are correct and identical.

- The subject product is not substantially similar or similar to Reg. No. 11556-117, because it contains the additional a.i. pyriproxyfen and the additional inert, [redacted].

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-Way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

READ ENTIRE LABEL BEFORE EACH USE

(Leaflet)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment for Dogs and
Puppies 7 Weeks and Older and 10 lbs and Under

READ ENTIRE LABEL BEFORE USE

For the Prevention and Treatment of Flea Infestation on Dogs.

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine ..	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

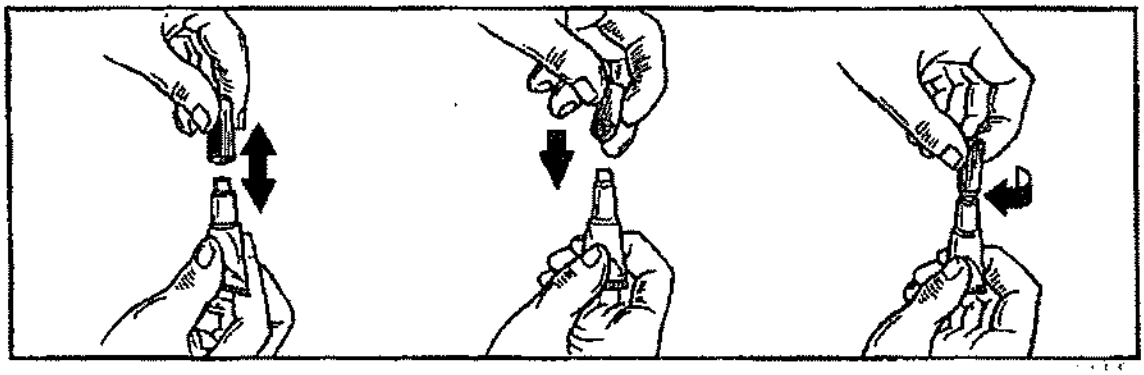
To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY

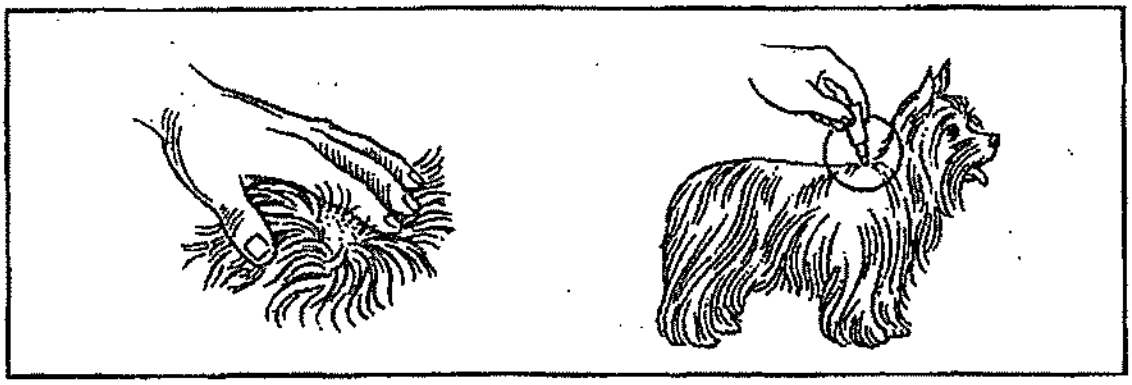
1. Use only on dogs. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

   Do not get this product in your pet's eyes or mouth.



7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal:** Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal:** Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

EPA Est. 11556-DEU-1

EPA Reg. No. 11556-~~XXX~~REI

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

NJFT

B

Please read instructions on reverse before completing form.

Form Approved. OMB No. 2070-0060. Approval expires 2-28-95

United States
Environmental Protection Agency
Washington, DC 20460

- [x] **Registration**
- [ ] **Amendment**
- [ ] **Other**

OPP Identifier Number: 270767

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification
11556-~~EIX~~ REI	Dr. Tina Levine	[x] None [ ] Restricted
4. Company/Product (Name)	**PM#**	
Advantage Plus 10 for Dogs	04	

5. Name and Address of Applicant *(Include ZIP Code)*
Bayer Corporation, Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

[ ] *Check if this is a new address*

6. Expedited Review. In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:
EPA Reg. No. _____
Product Name _____

Section - II

- [ ] Amendment - Explain below.
- [ ] Resubmission in response to Agency letter dated _____
- [ ] Notification - Explain below.
- [ ] Final printed labels in response to Agency letter dated _____
- [ ] "Me Too" Application.
- [x] Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section f and Section fl.)

See Attachment

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
[ ] Yes [x] No	[ ] Yes [x] No	[ ] Yes [x] No	[ ] Metal [x] Plastic [ ] Glass [x] Paper [ ] Other (Specify)
* *Certification must be submitted*	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information: [x] Label [ ] Container

4. Size(s) Retail Container: Four 0.4 ml tubes and Six 0.4 ml tubes

5. Location of Label Directions: [x] On Label [x] On Label accompanying product

6. Manner in Which Label is Affixed to Product: [ ] Lithograph [ ] Paper glued [ ] Stenciled [x] Other See Application text

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)
F. Terry McNamara	Manager, Preclinical Development	(913) 266-2588

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowlingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

2. Signature	3. Title	6. Date Application Received (Stamped)
F. Terry McNamara	Manager, Preclinical Development	
4. Typed Name	**5. Date**	
F. Terry McNamara	April 7, 2000	

EPA Form 8570-1 (Rev. 3-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060

EPA

United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number
270789

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification ☐ None ☐ Restricted
4. Company/Product (Name)	PM#	

5. Name and Address of Applicant *(Include ZIP Code)*

☐ *Check if this is a new address*

6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to:

EPA Reg. No. _____

Product Name _____

Section - II

☐ Amendment - Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
☐ "Me Too" Application.
☐ Other - Explain below.

Explanation: Use additional page(s) if necessary. (For section I and Section II.)

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes* ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Metal ☐ Plastic ☐ Glass ☐ Paper ☐ Other (Specify) _____
Certification must be submitted	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☐ Label ☐ Container		☐ On Label ☐ On Labeling accompanying product

6. Manner in Which Label is Affixed to Product ☐ Lithograph ☐ Paper glued ☐ Stenciled ☐ Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

2. Signature	3. Title	6. Date Application Received (Stamped)
4. Typed Name	5. Date	

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

PAPERWORK REDUCTION ACT NOTICE and INSTRUCTIONS

PAPERWORK REDUCTION ACT NOTICE: Public reporting burden for this collection of information is estimated to average 0.85 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, (2136), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

INSTRUCTIONS: This form is to be used for all applications for new registration, end use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

1. Certification with Respect to Citation of Data (EPA Form 9570-29). [If not exempted by 40 CFR 152.81 (b) (4)];
2. Confidential Statement of Formula (EPA Form 8570-4);
3. Formulator's Exemption Statement (EPA Form 8570-27);
4. Five copies of draft labeling;
5. Three copies of any data submitted;
6. Authorization letter where applicable;
7. Matrices where applicable.

Submission of Labeling - Labeling should first be submitted in the form of draft labels with all applications for new registration. Such draft labels may be in the form of typed label text on 8.5 x 11 inch paper for submission or a mockup of the proposed label. If prepared for mockup, it should be constructed in a way as to facilitate storage in an 8.5 x 11 inch file. Mockup labels significantly smaller than 8.5 x 11 inches should be mounted on 8.5 x 11 inch paper for submission.
Submission of Data - Data submitted in support of this application must be submitted in accordance with PR Notice 86-5.

SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.
Block A - Check the appropriate action for which you are submitting this form.

SECTION I - This section must be completed, as applicable, for all registration actions.

1. Company/Product Number - Insert your Company Number, if one has been assigned by EPA. This number may have been assigned to you as a basic registrant, a distributor, or as an establishment. If your product is registered, insert the Product Number.
2. EPA Product Manager - If known, fill in the name and PM number of the EPA Product Manager.
3. Proposed Classification - Specify the proposed classification of this product.
4. Product Name - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. Name and Address of Applicant - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
6. Expedited Review - FIFRA section 3 (c) 3 (B) provides for expedited review of applications for registration, or amendments to existing registrations, that are similar or identical to other pesticide products that are currently registered with the EPA. In order for your application to be eligible for expedited review, you must provide us with the EPA Registration Number and product name of the product you believe is similar to or identical to your product. The product must be similar or identical in both formulation and labeled uses.

SECTION II - This section must be completed for all applications submitted to amend the registration only of a currently registered product [Amendment], for a resubmission in response to an Agency letter, for notifications to the Agency, for the submission of final printed labeling, for reregistration and for any other action that pertains to a specific EPA-registered product. This section is not to be used for a new application for registration.

1. Subject of submission - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose[s] for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a separate page if additional space is needed.

SECTION III [Packaging and Container Information] - This Section must be completed for all applications submitted in connection with new registration or applicable amendments.

1. Type of Packaging - Check the appropriate block if your product will be packaged in the indicated packaging types. Indicate the size of the individual packets and number per retail container.
2. Type of Retail Container - Indicate type of container in which product will be marketed.
3. Location of Net Contents - Indicate the location of the net contents information for your product.
4. Size[s] of Retail Container - Specify the net contents of all retail containers for your product.
5. Location of Use Directions - Indicate the location of the use directions for your product.
6. Manner in which label is affixed to product - Indicated the method product label is attached to retail container.

SECTION IV [Contact Point] - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

1-5. Self-explanatory.
6. EPA Use Only.

Please read instructions on reverse before completing form. Form Approved. OMB No. 2070-0060

United States
Environmental Protection Agency
Washington, DC 20460

☐ Registration
☐ Amendment
☐ Other

OPP Identifier Number
270789

Application for Pesticide - Section I

1. Company/Product Number	2. EPA Product Manager	3. Proposed Classification ☐ None ☐ Restricted
4. Company/Product (Name)	PM#	
5. Name and Address of Applicant *(Include ZIP Code)* ☐ *Check if this is a new address*	6. **Expedited Review.** In accordance with FIFRA Section 3(c)(3)(b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. _____ Product Name _____	

Section - II

☐ Amendment - Explain below.
☐ Resubmission in response to Agency letter dated _____
☐ Notification - Explain below.
☐ Final printed labels in response to Agency letter dated _____
☐ "Me Too" Application.
☐ Other - Explain below.

Explanation: Use additional pages if necessary. (For section I and Section II.)

Section - III

1. Material This Product Will Be Packaged In:

Child-Resistant Packaging	Unit Packaging	Water Soluble Packaging	2. Type of Container
☐ Yes* ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Metal ☐ Plastic ☐ Glass ☐ Paper ☐ Other (Specify) _____
*Certification must be submitted	If "Yes" Unit Packaging wgt. / No. per container	If "Yes" Package wgt / No. per container	

3. Location of Net Contents Information	4. Size(s) Retail Container	5. Location of Label Directions
☐ Label ☐ Container		☐ On Label ☐ On Labeling accompanying product

6. Manner in Which Label is Affixed to Product ☐ Lithograph ☐ Paper glued ☐ Stenciled ☐ Other _____

Section - IV

1. Contact Point *(Complete items directly below for identification of individual to be contacted, if necessary, to process this application.)*

Name	Title	Telephone No. (Include Area Code)

Certification

I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

2. Signature	3. Title	6. Date Application Received (Stamped)
4. Typed Name	5. Date	

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete. White - EPA File Copy (original) Yellow - Applicant Copy

PAPERWORK REDUCTION ACT NOTICE and INSTRUCTIONS

PAPERWORK REDUCTION ACT NOTICE: Public reporting burden for this collection of information is estimated to average 0.85 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, (2136), U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460.

INSTRUCTIONS: This form is to be used for all applications for new registration, end use reregistration, amendment, resubmission, to applications for notifications, final printed labeling, reregistration, etc. In order to process an application for a new registration submitted on this form, the following material must accompany the application:

1. Certification with Respect to Citation of Data (EPA Form 8570-29). [If not exempted by 40 CFR 152.81 (b) (4)];
2. Confidential Statement of Formula (EPA Form 8570-4);
3. Formulator's Exemption Statement (EPA Form 8570-27);
4. Five copies of draft labeling;
5. Three copies of any data submitted;
6. Authorization letter where applicable;
7. Matrices where applicable.

Submission of Labeling - Labeling should first be submitted in the form of draft labels with all applications for new registration. Such draft labels may be in the form of typed label text on 8.5 x 11 inch paper for submission or a mockup of the proposed label. If prepared for mockup, it should be constructed in a way as to facilitate storage in an 8.5 x 11 inch file. Mockup labels significantly smaller than 8.5 x 11 inches should be mounted on 8.5 x 11 inch paper for submission.
Submission of Data - Data submitted in support of this application must be submitted in accordance with PR Notice 86-5.

SPECIFIC INSTRUCTIONS: Please read the instructions listed below before completing this application. First determine the type of registration action, listed in Block A, for which you are submitting this application. For applications submitted in connection with New Registration actions, Sections I, III, and IV must be completed by the applicant. For applications submitted in connection with amended reregistration actions, resubmissions, notifications, reregistrations, etc., Sections I, II, and IV must be completed by the applicant.
Block A - Check the appropriate action for which you are submitting this form.

SECTION I - This section must be completed, as applicable, for all registration actions.

1. Company/Product Number - Insert your Company Number, if one has been assigned by EPA. This number may have been assigned to you as a basic registrant, a distributor, or as an establishment. If your product is registered, insert the Product Number.
2. EPA Product Manager - If known, fill in the name and PM number of the EPA Product Manager.
3. Proposed Classification - Specify the proposed classification of this product.
4. Product Name - Enter the complete product name of this pesticide as it will appear on the label. The name must be specific to this product only. Duplication of names is not permitted among products of the same company. Do not include any brand name or company line designations.
5. Name and Address of Applicant - The name of the firm or person and address shown in your application is the person or firm to whom the registration will be issued. If you are acting in behalf of another party, you must submit authorization from that party to act for them in registration matters. An applicant not residing in the United States must have an authorized agent residing in the United States to act for them in all registration matters. The name and complete mailing address of such an agent must accompany this application.
6. Expedited Review - FIFRA section 3 (c) 3 (B) provides for expedited review of applications for registration, or amendments to existing registrations, that are similar or identical to other pesticide products that are currently registered with the EPA. In order for your application to be eligible for expedited review, you must provide us with the EPA Registration Number and product name of the product you believe is similar to or identical your product. The product must be similar or identical in both formulation and labeled uses.

SECTION II - This section must be completed for all applications submitted to amend the registration only of a currently registered product (Amendment), for a resubmission in response to an Agency letter, for notifications to the Agency, for the submission of final printed labeling, for reregistration and for any other action that pertains to a specific EPA-registered product. This section is not to be used for a new application for registration.

1. Subject of submission - Check the applicable block and provide the Agency letter date if appropriate. Provide a brief explanation of the purpose(s) for the submission, such as "the addition of a site, pest or crop (specify)"; "amend the Confidential Statement of Formula by..."; "reregistration submission"; "general label revision of use directions." Attach a seperate page if additional space is needed.

SECTION III (Packaging and Container Information) - This Section must be completed for all applications submitted in connection with new registration or applicable amendments.

1. Type of Packaging - Check the appropriate block if your product will be packaged in the indicated packaging types. Indicate the size of the individual packets and number per retail container.
2. Type of Retail Container - Indicate type of container in which product will be marketed.
3. Location of Net Contents - Indicate the location of the net contents information for your product.
4. Size(s) of Retail Container - Specify the net contents of all retail containers for your product.
5. Location of Use Directions - Indicate the location of the use directions for your product.
6. Manner in which label is affixed to product - Indicated the method product label is attached to retail container.

SECTION IV (Contact Point) - This Section must be completed for all applications for Registration actions, i.e., new products registration, resubmission, "me-too," reregistration, etc.

1-5. Self-explanatory.
6. EPA Use Only.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

04/13/2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Bayer Corporation, Animal Health, Agriculture Division
P.O. Box 390
Shawnee Mission, KS 66201

PRODUCT NAME: Advantage Plus 10 for Dogs
COMPANY NAME: Bayer Corporation, Animal Health, Agriculture Division
OPP IDENTIFICATION NUMBER: 270789
EPA FILE SYMBOL: 11556-REI
EPA RECEIPT DATE: 04/12/00

SUBJECT: RECEIPT OF APPLICATION FOR A NEW REGISTRATION

DEAR REGISTRANT:

The Office of Pesticides Programs has received your application for a new registration and it has passed an administrative screen for completeness.

Please note that this is only a notification of receipt of your application. This is only the first step in the application process, and does NOT constitute approval.

If you have any questions, please contact the Insecticide /Rodenticide Branch, at (703)-305-5404.

Sincerely,

Front End Processing Staff
Information Resources & Services Division
Information Services Branch

Bayer

April 7, 2000

Agriculture Division

Crop Protection Products

Bayer Corporation
8400 Hawthorn Road
P.O. Box 4913
Kansas City, MO 64120-0013
Phone: 816 242-2000

Ms. Dani Daniel
Registration Division (H7505C)
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: **Letter of Authorization; BAYER Animal Health**
ADVANTAGE Plus® Applications for Registration, Imidacloprid

Dear Ms. Daniel,

BAYER Corporation, Agriculture Division, hereby authorizes the Agency to refer to any research and/or test data on our active ingredient imidacloprid (the active ingredient in ADMIRE® and PROVADO®) in support of the applications for registration of ADVANTAGE Plus® 10, ADVANTAGE Plus® 20, ADVANTAGE Plus® 55, ADVANTAGE Plus® 100, ADVANTAGE Plus® 9, ADVANTAGE Plus® 18, submitted by BAYER Animal Health, 12707 W. 63rd St., Shawnee Mission, KS, 66216-1846.

Furthermore, the Agriculture Division of BAYER Corporation has three business groups; Crop Protection, Specialty, and Animal Health. All three business groups seek product registrations for products containing the active ingredient imidacloprid. Any confidential business information released by the Agency in data evaluation records or other documents for company number 3125 (Crop Protection and Specialty Groups) can be disclosed without restriction to the Animal Health Group, company number 11556. In addition, the Agency is authorized to refer to any research and test data submitted under company number 3125 in support of applications for registration from BAYER Animal Health, company number 11556.

As always, if you have any questions, feel free to call me at (816) 242-2838.

Sincerely,

BAYER Corporation, Agriculture Division

James L. Kunstman
Manager, Product Registrations

Product ingredient source information may be entitled to confidential treatment

Form Approved. OMB No. 2070-0060. Approval Expires 5-31-98.

United States
Environmental Protection Agency
Washington, DC 20460

Formulator's Exemption Statement

(40 CFR 152.85)

Applicant's Name and Address	EPA File Symbol/Registration Number
Bayer Corporation Animal Health, Agriculture Division P. O. Box 390 Shawnee Mission, KS 66201	11556-~~xxx~~ REI
	Product Name Advantage Plus 10 for Dogs
	Date of Confidential Statement of Formula *(EPA Form 8570-4)* April 7, 2000

As an authorized representative of the applicant for registration of the product identified above, I certify that:

(1) This product contains the following active ingredient(s):

Pyriproxyfen
Imidacloprid (not citing Formulator's Exemption for this active ingredient)

(2) Of these, each active ingredient listed in paragraph (4) is present solely as the result of the use of that active ingredient in the manufacturing, formulation or repackaging another product which contains that active ingredient which is registered under FIFRA Section 3, is purchased by us from another producer, and is labeled for at least each use for which my product is proposed to be labeled.

(3) Indicate by checking (A) or (B) below which paragraph applies:

☑ (A) An accurate Confidential Statement of Formula *(EPA FORM 8570-4)* for the above identified product is attached to this statement. That formula statement indicates, by company name, registration number, and product name, the source of the active ingredient(s) listed in paragraph (1).

OR

☐ (B) The Confidential Statement of Formula (CSF) (EPA Form 8570-4) referenced above and on file with the EPA is complete, current, and accurate and contains the information required on the current CSF.

(4) The following active ingredients in this product qualify for the formulator's exemption.

Source

Active Ingredient	Product Name	Registration Number
Pyriproxyfen	[redacted]	[redacted]

Signature	Name and Title	Date
F. T. McNamara	F. T. McNamara Mgr, Preclinical Dev.	April 7, 2000

EPA Form 8570-27 (Rev. 8-95)

White - EPA copy
Yellow - Applicant copy

★ U.S. GPO: 1998-656-620/20475

Form Approved OMB No. 2070-0060

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460

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Do not send the completed form to this address.

Certification with Respect to Citation of Data

Applicant's/Registrant's Name, Address, and Telephone Number	EPA Registration Number/File Symbol
Bayer Corporation, Animal Health, Agriculture Division P.O. Box 390 Shawnee Mission, KS 66201	11556-~~xxx~~ REZ
Active Ingredient(s) and/or representative test compound(s): Pyriproxifen; Imidacloprid	Date: April 7, 2000
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158): Indoor, Non-food	Product Name: ADVANTAGE PLUS 10 for Dogs

NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).

☐ I am responding to a Data-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

SECTION I: METHOD OF DATA SUPPORT (Check one method only)

☐ I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).

☑ I am using the selective method of support (or cite-all option under the selective method), and have included with this form a completed list of data requirements (the Data Matrix form must be used).

SECTION II: GENERAL OFFER TO PAY

(Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements)

☐ I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.

SECTION III: CERTIFICATION

I certify that this application for registration, this form for reregistration, or this Data-Call-In response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses .

I certify that for each exclusive use study cited in support of this registration or reregistration, that I am the original data submitter or that I have obtained the written permission of the original data submitter to cite that study.

I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.

I certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.

I certify that the statements I have made on this form and all attachments to it are true, accurate, and complete. I acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both under applicable law.

Signature	Date	Typed or Printed Name and Title
F. Terry McNamara	April 7, 2000	F. Terry McNamara Mgr, Preclinical Development

EPA Form 8570-34 (9-97) Electronic and Paper versions available. Submit only Paper version.

MGK®
McLAUGHLIN GORMLEY KING COMPANY
8810 Tenth Avenue North • Minneapolis, Minnesota 55427-4372 U.S.A.

April 3, 2000

Mr. Marion Johnson (PM 10)
Office of Pesticide Programs (H7505C)
U.S. ENVIRONMENTAL PROTECTION AGENCY
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington DC 20460

Subject: Bayer Animal Health
9009 W. 67th Street, Bldg. 1
Merriam, KS 66202

Dear Mr. Johnson:

This letter serves as authorization, in accordance with our agreement with the registrant, to refer to the following data submitted by McLaughlin Gormley King Company to EPA for the subject company's registration.

MGK Efficacy Data: Submitted to EPA Reg. No. 1021-1619 on March 30, 2000

Registrant's Product: Advantage Plus® 10
EPA Reg. No.: 11556- REI

Although this is authorization to rely on MGK data for the subject company's subject registration, absolutely no data of a confidential nature is to be disclosed to them.

Sincerely,

McLAUGHLIN GORMLEY KING COMPANY

Julie B. Schlekau

Julie B. Schlekau
Registration Specialist

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

DATA MATRIX

Date: April 7, 2000	EPA Reg No./File Symbol: 11556-~~XXX~~, 11556-XXX 11556-XXX, 11556-XXX	Page 1 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	Product: Advantage Plus® 10 for Dogs Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
Product Chemistry, Section 158.240						
61-1	Chemical identity	42055302	3125	PER	BR 1759 (TGAI)	
		43306001	3125	PER	BR 1879 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
61-2	Statement of Composition	42055302	3125	PER	BR 1759 (TGAI)	
		43306001	3125	PER	BR 1879 (TGAI)	
		42270801	3125	PER	BR 1785 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
61-3	Formation of impurities	42055302	3125	PER	BR 1759 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
62-1	Preliminary analysis	42055303	3125	PER	BR 1760 (TGAI)	
		43306002	3125	PER	BR 1880 (TGAI)	
		42270802	3125	PER	BR 1786 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
62-2	Certification of limits	42055303	3125	PER	BR 1760 (TGAI)	
		43306002	3125	PER	BR 1880 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
62-3	Analytical method	42055303	3125	PER	BR 1760 (TGAI)	
		43213001	3125	PER	BR 1874 (TGAI)	
		43306002	3125	PER	BR 1880 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
			11556	OWN	Report No. 75130	Submitted with application for Advantage Plus® 9 for Cats

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

DATA MATRIX REI

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~, 11556-XXX 11556-XXX, 11556-XXX	Page 2 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 10 for Dogs Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
63-1	Chemical and Physical Properties	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-2	Appearance	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-3	Physical state	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-4	Odor	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-5	Melting point	42055304	3125	PER	BR 1761 (TGAI)	
63-6	Boiling point	42055304	3125	PER	BR 1761(TGAI)	
63-7	Density	42055304	3125	PER	BR 1761 (TGAI)	
		43356302	3125	PER	BR 1761 (Formulation)	
63-8	Solubility	42055304	3125	PER	BR 1761 (TGAI)	
63-9	Vapor pressure	42055304	3125	PER	BR 1761 (TGAI)	
63-10	Dissociation constant					N.A. - Does not dissociate
63-11	Octanol / water partition	42055304	3125	PER	BR 1761 (TGAI)	
63-12	pH	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-13	Stability	42055304	3125	PER	BR 1761 (TGAI)	
63-14	Oxidizing / reducing action		3125	PER		N.A. - No oxidative or reductive characteristics
63-15	Flammability	42055304	3125	PER	BR 1761 (TGAI)	
63-16	Explodability	42055304	3125	PER	BR 1761 (TGAI)	

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

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DATA MATRIX REF.

Date: April 7, 2000	EPA Reg No./File Symbol: 11556-~~XXX~~; 11556-XXX 11556-XXX, 11556-XXX	Page 3 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	Product: Advantage Plus® 10 for Dogs ✓ Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
63-17	Storage stability	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-18	Viscosity		3125	PER		N.A. - Solid
63-19	Miscibility		3125	PER		N.A. - Solid
63-20	Corrosion characteristics	42055304	3125	PER	BR 1761 (TGAI)	
		42256302	3125	PER	BR 1766 (Formulation)	
63-21	Dielectric breakdown volt					N.A.- Solid
64-1	Submittal of samples				Samples available upon request	
830-Group A	Product Chemistry: Identity, Composition, Analysis		11556	OWN	Report No. 75133	Submitted with application for Advantage Plus® 9 for Cats
830-Group B	Product Chemistry: Physical/Chemical Properties		11556	OWN	Report No. 75132	Submitted with application for Advantage Plus® 9 for Cats
Wildlife and Aquatic Organisms, Section 158.490						
71-1	Acute avian oral - quail/duck					N.A.
71-2(a)	Avian dietary - quail					N.A.
71-2(b)	Avian dietary - duck					N.A.
71-3	Wild mammal toxicity					N.A.
71-4(a)	Avian reproduction - quail					N.A.
71-4(b)	Avian reproduction - duck					N.A.
71-5	Simulated or actual field study					N.A.
72-1(a)	Fish toxicity - bluegill					N.A.
72-1(b)	Fish toxicity bluegill - tcp					N.A.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

DATA MATRIX

REJ

Date: April 7, 2000	EPA Reg No./File Symbol: 11556-~~XXX~~, 11556-XXX 11556-XXX, 11556-XXX	Page 4 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	Product: Advantage Plus® 10 for Dogs Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
72-2(a)	Invertebrate toxicity - Daphnia					N.A.
72-2(b)	Invertebrate toxicity - Amphipods					N.A.
72-2(c)	Acute aquatic invertebrate toxicity - Chironomids					N.A.
72-3(a)	Estuarine / marine toxicity - fish					N.A.
72-3(b)	Estuarine / marine toxicity - mollusk					N.A.
72-3(c)	Estuarine/marine toxicity - shrimp					N.A.
72-4(a)	Early life stage - fish					N.A.
72-4(b)	Life cycle invertebrate					N.A.
72-7	Simulated or actual field study					N.A.
None	Foliar half-life and distribution for potatoes					N.A.
None	Runoff and Erosion predictions for apple/potato/cotton					N.A.
None	Risk assessment for apple/potato/cotton					N.A.
None	PELMO Modeling - sugarbeet/Germany					N.A.
Toxicology, Section 158.340						
		42055331	3125	PER	Report No. 100040 (TGAI)	
		42256313	3125	PER	Report No. 100010 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679601	1156	OWN	Report No. 74585 (Adv)	
81-1	Acute oral toxicity rat		11556	OWN	Report No. 75195 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

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DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~, 11556-XXX 11556-XXX, 11556-XXX	Page 5 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 10 for Dogs Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
		42055332	3125	PER	Report No. 100041 (TGAI)	
		42256315	3125	PER	Report No. 100002 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F	
		4379602	11556	OWN	Report No. 74584 (Adv)	
81-2	Acute dermal toxicity, rat/rabbit		11556	OWN	Report No. 75196	Submitted with application for Advantage Plus® 9 for Cats
		42055333	3125	PER	Report No. 99806 (TGAI)	
		42286101	3125	PER	Report No. 99806-1 (TGAI)	
		42256317	3125	PER	Report No. 100012 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679603	11556	OWN	Report No. 74589 (Adv)	
81-3	Acute inhalation toxicity, rat		11556	OWN	Report No. 75197 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats
		42055334	3125	PER	Report No. 99679 (TGAI)	
		42256319	3125	PER	Report No. 99815 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679604	11556	OWN	Report No. 74588 (Adv)	
81-4	Primary eye irritation - rabbit		11556	OWN	Report No. 75199 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats

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Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~, 11556-XXX 11556-XXX, 11556-XXX	Page 6 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 10 for ~~Dogs~~ Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
		42055335	3125	PER	Report No. 99804 (TGAI)	
		42256321	3125	PER	Report No. 99816 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679605	11556	OWN	Report No. 74586 (Adv)	
81-5	Primary dermal irritation - rabbit		11556	OWN	Report No. 75200 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats
		42055336	3125	PER	Report No. 99800 (TGAI)	
		42256323	3125	PER	Report No. 100003 (2 F)	
		43428201	3125	PER	Report No. 106380 (1.6 F)	
		43679606	11556	OWN	Report No. 74587 (Adv)	
81-6	Dermal sensitization - guinea pig		11556	OWN	Report No. 75201 (Adv Plus)	Submitted with application for Advantage Plus® 9 for Cats
		43170301	3125	PER	Report No. 106348	
81-8(SS)	Acute neurotoxicity	43285801	3125	PER	Report No. 106348-1	
82-1(a)	90-day feeding - rodent	42256327	3125	PER	Report No. 100036	
82-1(b)	90-day feeding - non-rodent	42256328	3125	PER	Report No. 100176	
82-2	21-day dermal - rabbit/rat	42256329	3125	PER	Report No. 100688	
82-5(b)	90 day neurotoxicity - mammal	43286401	3125	PER	Report No. 106356	
		42256331	3125	PER	Report No. 100652	
		42256332	3125	PER	Report No. 101931	
		42256333	3125	PER	Report No. 102658	
83-1(a)	Chronic feeding toxicity - rodent	42256334	3125	PER	Report No. 99672	
83-1(b)	Chronic feeding toxicity - non-rodent	42273002	3125	PER	Report No. 100015	

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Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	Product: Advantage Plus® 10 for Dogs Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
		42256331	3125	PER	Report No. 100652	
		42256332	3125	PER	Report No. 101931	
		42256333	3125	PER	Report No. 102658	
83-2(a)	Oncogenicity - rat	42256334	3125	PER	Report No. 99672	
		42256335	3125	PER	Report No. 100693	
		42256336	3125	PER	Report No. 101929	
83-2(b)	Oncogenicity - mouse	42256337	3125	PER	Report No. 99808	
83-3(a)	Developmental toxicity - rat	42256338	3125	PER	Report No. 98571	
83-3(b)	Developmental toxicity - rabbit	42256339	3125	PER	Report No. 98572	
83-4	Two generation reproduction - rat	42256340	3125	PER	Report No. 100647	
		42256341	3125	PER	Report No. 101276	
		42256342	3125	PER	Report No. 98584	
84-2(a)	Gene mutation (ames test)	42256343	3125	PER	Report No. 98570	
		42256344	3125	PER	Report No. 100021	
		42256345	3125	PER	Report No. 99262	
		42256346	3125	PER	Report No. 99257	
		42256347	3125	PER	Report No. 102652	
	Structural chromosomal aberration	42256348	3125	PER	Report No. 102654	
84-2(b)		42256349	3125	PER	Report No. 102655	
		42256350	3125	PER	Report No. 99676	
		42256351	3125	PER	Report No. 101275	
		42256352	3125	PER	Report No. 98573	
84-4	Other genotoxic effects	42256353	3125	PER	Report No. 102653	

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Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 10 for Dogs Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
		42256354	3125	PER	Report No. 101999	
		42256355	3125	PER	Report No. 87264	
		42256356	3125	PER	Report No. 87265	
85-1	General metabolism	42256357	3125	PER	Report No. 102617	
		43679607	11556	OWN	Report No. 74580 (Adv)	Dogs
		43679608	11556	OWN	Report No. 74590 (Adv)	Dogs
870.7200		44099801	11556	OWN	Report No. 74730 (Adv)	Puppies
			11556	OWN	Report No. 75121 (Adv Plus)	Dogs, Submitted with this application
(86-1)	Domestic Animal Safety		11556	OWN	Report No. 75119 (Adv Plus)	Puppies, Submitted with this application
		43679503	11556	OWN	Report No. 74571 (Adv)	Cats
		43679504	11556	OWN	Report No. 74581 (Adv)	Cats
		43679609	11556	OWN	Report No. 74572 (Adv)	Dogs
		43679610	11556	OWN	Report No. 74541 (Adv)	Dogs
		44256901	11556	OWN	Report No. 74800 (Adv)	Speed of flea kill
		44256902	11556	OWN	Report No. 47828 (Adv)	Larvicidal efficacy
		44256903	11556	OWN	Report No. 74792 (Adv)	Effects of shampooing
			1021	PER	Report No. OT018-94	Pyriproxyfen efficacy
			1021	PER	Report No. OT016-93	Pyriproxyfen efficacy
			1021	PER	Report No. OT006-96	Pyriproxyfen efficacy
95-9	Efficacy		1021	PER	Report No. OT023-93	Pyriproxyfen efficacy
Plant Protection, Section 158.540						
122-2	Aquatic plant growth					N.A.
123-2	Aquatic plant growth					N.A.

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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
Non-Target Insects, Section 158.590						
141-1	Honey bee acute contact					N.A.
141-2	Honey bee residue on foliage					N.A.
Reentry Protection, Section 158.390						
230-236	Mixer/loader/applicator exposure					N. A.
Environmental Fate, Section 158.290						
161-1	Hydrolysis					N.A.
161-2	Photodegradation - water					N.A.
161-3	Photodegradation - soil					N.A.
162-1	Aerobic soil metabolism					N.A.
162-2	Anerobic soil metabolism					N.A.
162-3	Anaerobic aquatic metabolism					N.A.
163-1	Leaching / adsorption/desorption					N.A.
164-1	Terrestrial field dissipation					N.A.
165-1	Confined rotational crop					N.A.
165-2	Field rotational crop					N.A.
166-1	Ground water - small prospective					N.A.
None	Environmental fate summary					N.A.

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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
Residue, Section 158.240						
171-4(a)	Nature of residue - plants					N.A.
171-4(b)	Nature of residue - livestock and poultry					N.A.
171-4(c)	Residue analytical method - plants					N.A.
171-4(d)	Residue analytical method - animal					N.A.
171-4(e)	Storage stability					N.A.
171-4(j)	Magnitude of residues - meat/milk/poultry/egg					N.A.
171-4(k)	Magnitude of residue - crop field trials					N.A.
171-4(l)	Magnitude of residue - processed food/feed					N.A.
171-4(m)	Method validation/ multiresidue method					N.A.
None	Benefits Reports					
None	Dietary Analysis					N.A.

Signature F. Terry McNamara

F. Terry McNamara
Manager, Preclinical Development

April 7, 2000

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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description
[redacted]			3125	PER		
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			3125	PER		
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats

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[redacted]			3125	PER	[redacted]	
			3125	PER		
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			3125	PER		
			3125	PER		
			3125	PER		
						N.A. - Does not dissociate
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		N.A. - No oxidative or reductive characteristics
			3125	PER		
			3125	PER		

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			3125	PER		
			3125	PER		
			3125	PER		N.A. - Solid
			3125	PER		N.A. - Solid
			3125	PER		
			3125	PER		
						N.A. - Solid
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
[redacted]					[redacted]	N.A.
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			1156	OWN		
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats

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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
[redacted]			3125	PER		
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			11556	OWN		
			11556	OWN		Submitted with application for Advantage Plus® 9 for Cats
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Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
[redacted]			3125	PER	[redacted]	
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[redacted]			3125	PER		
			3125	PER		
			3125	PER		
			3125	PER		
			11556	OWN		Dogs
			11556	OWN		Dogs
			11556	OWN		Puppies
			11556	OWN		Dogs. Submitted with this application
			11556	OWN		Puppies. Submitted with this application
			11556	OWN		Cats
			11556	OWN		Cats
			11556	OWN		Dogs
			11556	OWN		Dogs
			11556	OWN		Speed of flea kill
			11556	OWN		Larvicidal efficacy
			11556	OWN		Effects of shampooing
			1021	PER		Pyriproxyfen efficacy
			1021	PER		Pyriproxyfen efficacy
			1021	PER		Pyriproxyfen efficacy
			1021	PER		Pyriproxyfen efficacy
						N.A.
						N.A.

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DATA MATRIX

Date: April 7, 2000	**EPA Reg No./File Symbol:** 11556-~~XXX~~ REZ, 11556-XXX 11556-XXX, 11556-XXX	Page 9 of 10
Bayer Corporation - Agriculture Division, Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390	**Product:** Advantage Plus® 10 for Dogs Advantage Plus® 20 for Dogs Advantage Plus® 55 for Dogs Advantage Plus® 100 for Dogs	**Ingredient:** Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1

Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note: Report Number	Note: Description
[redacted]						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.
						N.A.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
401 M Street, S.W.
WASHINGTON, D.C. 20460 Form

Approved OMB No. 2070-0060

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						N.A.
						N.A.
						N.A.
						N.A.
						N.A.

Signature F. Terry McNamara

F. Terry McNamara
Manager, Preclinical Development

April 7, 2000

09-21-4

x:mtoiij/EPAdmmatrix/AdvantagePlusDogsPUBLIC.doc

Product ingredient source information may be entitled to confidential treatment

ATTACHMENT
FOR
APPLICATION FOR PESTICIDE REGISTRATION

Advantage Plus® 10 for Dogs

With this application form and the enclosed documents, Bayer Corporation requests the registration of Advantage Plus® 10 for Dogs, a new insecticide product.

Briefly, this product will consist of a blister package constructed of cardboard, plastic and foil containing individual plastic tubes each containing 0.4 ml of the liquid insecticide. There will be two package sizes – a 4-tube package and a 6-tube package. The blister package containing the tubes will be placed in a cardboard box. The box will contain all of the draft labeling text, dated 4/7/2000, which is enclosed (5 copies each), except for directions for use. The complete label text, including directions for use, will be included in a leaflet insert that will accompany the blister package in the cardboard box. The individual plastic tubes inside the blisters will contain only the draft labeling indicated on page 8 of the label text, again dated 4/7/2000, which is enclosed (5 copies each). Please note, because the tubes are very small in size, we are proposing that only the product name, the active ingredients, the amounts of the active ingredients and the EPA Reg. No. be printed onto each tube (again, the overall blister package will contain complete labeling). Also note, this packaging and labeling scheme is identical to that used by Bayer's currently registered product, Advantage® 10 for Dogs (EPA Reg. No. 11556-117).

PRODUCT CHEMISTRY.

The insecticide formulation is a liquid solution of imidacloprid (9.1% w/w) and pyriproxyfen (0.46% w/w) in inert ingredients which are on EPA's list of acceptable inert ingredients for use in pesticides. Two (2) copies of the Confidential Statement of Formula (CSF) for this product are enclosed. The source of the active ingredients for this product are [redacted]. The product chemistry data to support the registration of this new formulation are in the following Bayer Reports:

Bayer Report No. 75133 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Topical Solution – OPPTS 830 – Group A: Product Identity, Composition, and Analysis",

Bayer Report No. 75132 entitled "Product Chemistry of (10% w/v, 9.1% w/w) Imidacloprid + (0.5% w/v, 0.46% w/w) Pyriproxyfen Water Topical Solution, OPPTS 830 Group B – Physical/Chemical Properties" and,

Bayer Report No. 75130 entitled "Validation of Bayer Animal Health Test Method TMC-14.02 for the Determination of Imidacloprid and Pyriproxyfen Topical Solution Formulation by HPLC."

Three (3) copies of each of these reports accompany the application for Advantage Plus® 9 for Cats. Although the report titles do not use the "Advantage Plus" trade name, the formulation described and tested is Advantage Plus® 10 for Dogs.

TOXICOLOGY

Also enclosed with the Advantage Plus® 9 for Cats application are three (3) copies of the following six reports describing the results of Guideline 870.1100 through 870.2600 acute toxicology testing:

EPA Guideline Number	Bayer Report Number	Bayer Report Title
870.1100	75195	Acute Oral Toxicity Study with Imidacloprid (9.1%) /Pyriproxyfen (0.9%) Spot On in Rats
870.1200	75196	Acute Dermal Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats
870.1300	75197	Acute 4-Hour Inhalation Toxicity Study with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On in Rats
870.2400	75199	Primary Eye Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%)/5.0% Water Spot On
870.2500	75200	Primary Dermal Irritation Study in Rabbits with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On
870.2600	75201	Dermal Sensitization Study in Guinea Pigs – Closed Patch Technique with Imidacloprid (9.1%)/Pyriproxyfen (0.9%) Spot On

Please note, the study titles refer to test materials with a slightly different formulation than that which is proposed for registration. The formulation proposed for registration contains 9.1% imidacloprid, 0.46% pyriproxyfen, and [redacted], and the other inert ingredients identified on the enclosed Confidential Statement of Formula. The formulation used for five of the acute toxicity studies contained 9.1% imidacloprid and a higher pyriproxyfen concentration (0.9%) and no [redacted]. The formulation used for the primary eye irritation study (Bayer Report No. 75199) contained 9.1% imidacloprid, 0.9% pyriproxyfen, and [redacted] (please note the study title states 5% water and the formulation was 5% water on a volume/volume basis, but on a weight/weight basis, the [redacted] concentration is [redacted] as documented in the Confidential Appendix to Report No. 75199). These studies are being submitted in support of the registration for the formulation with 0.46% pyriproxyfen. As per EPA's November 2, 1999 meeting with Bayer, the Agency's technical reviewers (Byron Backus and John Redden) confirmed that EPA would accept these studies since the formulation tested represents a "worst case" compared to the current formulation proposed for registration.

The results of these toxicology studies demonstrate that the appropriate signal word is "CAUTION" for all six Advantage Plus® products. The toxicity categories based on the study results are summarized below.

Study Type	Bayer Report Number	Toxicity Category
Acute Oral	75195	III
Acute Dermal	75196	IV
Acute Inhalation	75197	IV
Primary Eye Irritation	75199	III
Primary Dermal Irritation	75200	IV
Dermal Sensitization	7520I	Negative

To address the Guideline 870.7200 (86-1) Domestic Animal Safety requirement for Advantage Plus® 10 for Dogs (and also Advantage Plus® 20, 55, and 100 for Dogs), three (3) copies of the 870.7200 report for adult dogs and three copies of the 870.7200 report for puppies are enclosed with this application. Specifically, copies of Bayer Report No. 75121 entitled "Evaluation of the General Safety of 9.1% (w/w) Imidacloprid with 0.9% (w/w) Pyriproxyfen Spot-on Formulation in the Target Species, Adult Dogs" and Bayer Report No. 75119 entitled "Evaluation of the General Safety of 9.1% (w/w) Imidacloprid with 0.9% (w/w) Pyriproxyfen Spot-On Formulation in the Target Species, Seven Week Old Puppies" are enclosed with this application.

Also, the above cited domestic animal safety studies support the registration of the other Advantage Plus® products for dogs - Advantage Plus® 20, 55, and 100 for Dogs - whose applications accompany this application.

EPA MRID 44256901 entitled "Comparative Evaluation of How Quickly Advantage® and Frontline™ (fipronil) Top Spot Kill Fleas on Dogs" (Bayer Report No. 74800).

Whereas Advantage® was efficacious against larval and adult fleas, the new Advantage Plus® product is effective against flea larvae, adult fleas, and flea eggs. The active ingredient, pyriproxyfen, is currently registered in at least 92 products for many different uses. Among these registrations, there are at least 13 currently registered pyriproxyfen flea products which range in active ingredient concentration from 0.125 to 5.3 percent. The concentration of pyriproxyfen in Advantage Plus® (0.46%) falls within the range of concentrations of the currently registered products.

Bayer is citing four efficacy studies for pyriproxyfen. [redacted]

"Evaluation of Two Concentrations of Nylar (Pyriproxyfen) in a Dip and Shampoo Formulation Against the Hatch of Flea Eggs Collected from Treated Cats" (MGK Report No. OT018-94),

"Flea Eggs: Target of the New IGR On-Animal Treatments" (MGK Report No. OT016-93),

"Final Report on Comparison of Isopropyl Alcohol Dilutions of Pyriproxyfen and Fenoxycarb on Hatchability of Flea Eggs" (MGK Report No. OT006-96) and,

"Final Report on the Physiological Effects of Pyriproxyfen on Adults and Eggs of the Cat Flea, *Ctenocephalides felis* (MGK Report No. OT023-93).

The results of these studies support the once-a-month application rate for Advantage Plus® since the efficacious concentration of pyriproxyfen used in the studies was lower than the concentration in the formulation proposed for registration. In addition, the lower concentration of pyriproxyfen was shown to be effective for a period greater than one month.

These efficacy study reports also support the registration of the other Advantage Plus® products for dogs - Advantage Plus® 20, 55, and 100 for Dogs - whose applications accompany this application.

EFFICACY

To support the claim of flea control for the Advantage Plus® 10 (and 20, 55, and 100) product(s) on dogs, Bayer is citing studies previously submitted to, reviewed by, and accepted by the Agency for Bayer's currently registered Advantage® 10, 20, 55, and 100 for Dogs (EPA Reg. Nos. 11556-117, -119, -120, -122) products. Specifically, these reports are:

EPA MRID 43679609 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74572) and,

EPA MRID 43679610 entitled "Efficacy Confirmation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Dogs" (Bayer Report No. 74541).

EPA MRID 43679503 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74571) and,

EPA MRID 43679504 entitled "Efficacy Evaluation of Bay t 7391 (Imidacloprid) 10% Solution Applied Dermally for Control of Fleas on Cats" (Bayer Report No. 74581).

The above referenced studies support the once-per-month use of imidacloprid (Advantage®) to control fleas and, therefore, the once-per-month use of imidacloprid in Advantage Plus® to control fleas.

The currently accepted labels for Advantage® 10, 20, 55, and 100 for Dogs and the draft proposed labels for Advantage Plus® 10, 20, 55, and 100 for Dogs have a claim for water resistance of the product, larvicidal efficacy, and a 12-hour "speed of kill" claim. These claims are supported by Bayer studies previously submitted to, reviewed by, and accepted by the Agency for Bayer's currently registered products Advantage® 10, 20, 55, and 100 for Dogs (EPA Reg. No. 11556-117, -119, -120, -122). Specifically, these reports are:

EPA MRID 44256903 entitled "Evaluation of the Effects of Shampooing or Water Immersion on the Initial and Residual Efficacy of Advantage® for Flea Control on Dogs" (Bayer Report No. 74792),

EPA MRID 44256902 entitled "Imidacloprid Topical Formulation: Larvicidal Effect Against *Ctenocephalides felis* in the Surroundings of Treated Dogs" (Bayer Report No. 74828) and,

DATA COMPENSATION

An appropriate data matrix listing all of the data necessary to support the registration of Advantage Plus® 10 (and also the other Advantage Plus® products for dogs) is enclosed with this application. Please note, the enclosed data matrix cites only those data necessary for this registration. This registration application is for a product used only on dogs (classified as an indoor, non-food use); the data matrix does not cite any imidacloprid environmental fate, ecological effects nor residue chemistry data because these data are not necessary for this proposed registration.

Generic Data

With regard to imidacloprid, the Crop Protection group of Bayer Corporation's Agriculture Division is the basic registrant of imidacloprid therefore, the Animal Health group cannot claim Formulator's Exemption for the generic data requirements. Accordingly, enclosed is a copy of Letter of Authorization from the other group (EPA Company No. 3125) of the Agriculture Division authorizing the use of the generic imidacloprid data by the Animal Health group (EPA Company No. 11556) of the Agriculture Division. These generic data are cited in the enclosed data matrix.

With regard to pyriproxyfen, a completed Formulator's Exemption form (EPA Form 8570-27) is enclosed with this application for Bayer to address compensation of pyriproxyfen generic data. Also, enclosed with this application is a Letter of Authorization from [redacted]

Product Specific Data

All of the data necessary to support the registration of Advantage Plus® 10 are data previously submitted by Bayer's Animal Health group (EPA Company No. 11556) or are enclosed with this application or were submitted by [redacted] Enclosed with this application is a Letter of Authorization from [redacted] All of these data are cited in the enclosed Data Matrix.

As demonstrated in the enclosed, completed Certification With Respect to Citation of Data (EPA Form 8570-29), we are choosing the Selective Method of Support for pyriproxyfen efficacy data. Again, a Letter of Authorization from [redacted] to cite these data is enclosed.

CHILD RESISTANT PACKAGING

Certification that the packaging for Advantage Plus® 10 meets the child-resistant packaging standards in 40 CFR 157.32 is not necessary because Advantage Plus® 10 does not meet any of the toxicity criterion listed in 40 CFR 157.22 (a) for products requiring child resistant packaging.

Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-Way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

READ ENTIRE LABEL BEFORE EACH USE

(Leaflet)

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If on skin: Wash with plenty of soap and water.

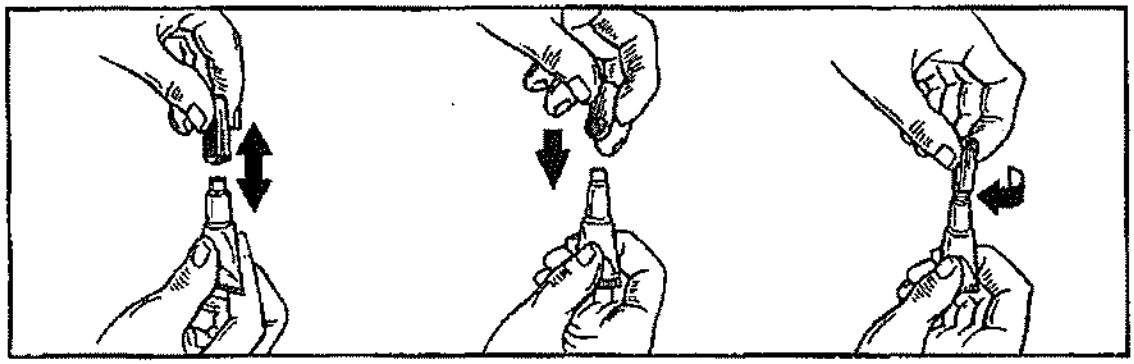
To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY

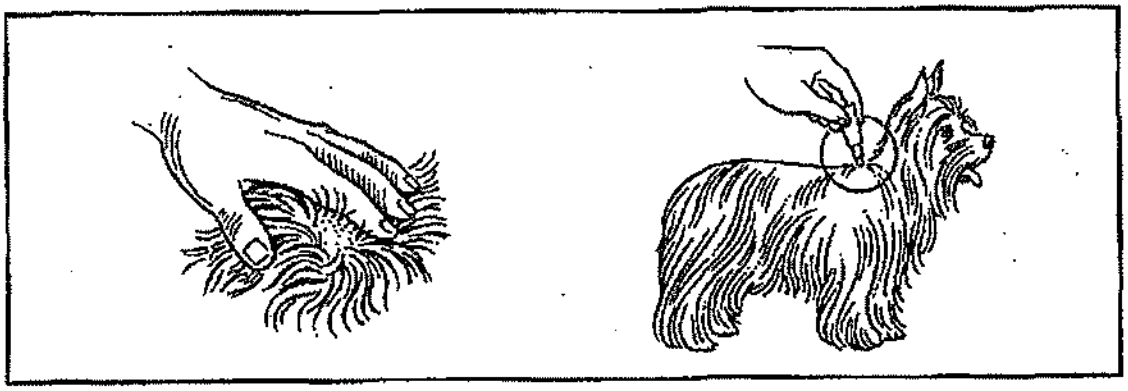
1. Use only on dogs. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

   Do not get this product in your pet's eyes or mouth.



7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal:** Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal:** Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

EPA Est. 11556-DEU-1

EPA Reg. No. 11556-~~XXX~~ REI

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

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Four 0.4 mL Tubes

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Manufactured For

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Animal Health
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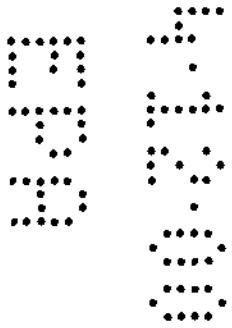
Made in Germany



(Back Panel)

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Multi-Stage Flea Control

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(Leaflet)

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For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

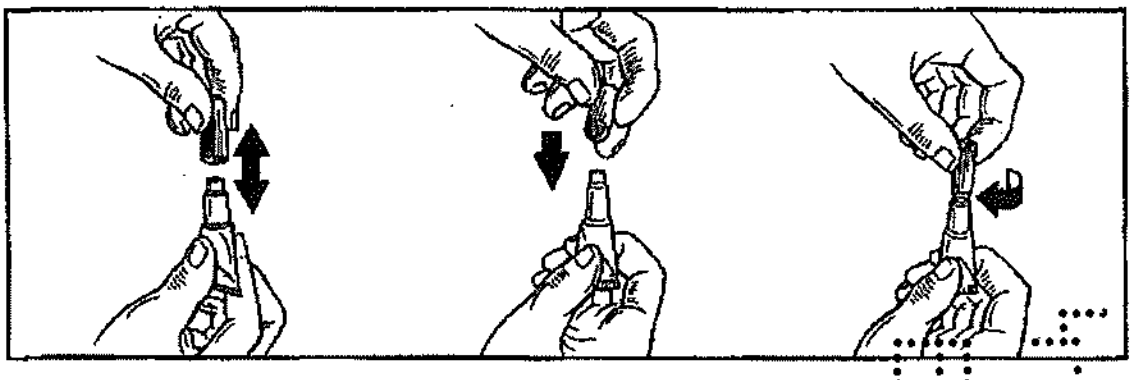
To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY

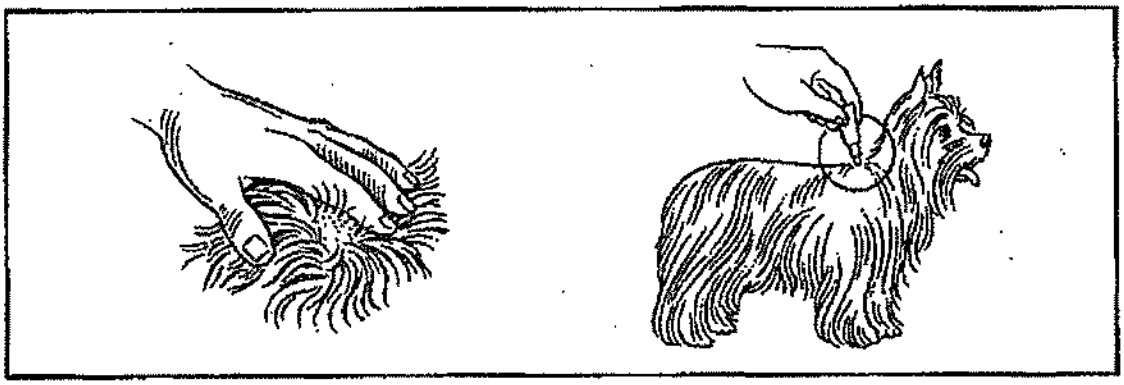
1. Use only on dogs. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

Do not get this product in your pet's eyes or mouth.



7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal**: Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal**: Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

EPA Est. 11556-DEU-1

EPA Reg. No. 11556-XXX

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

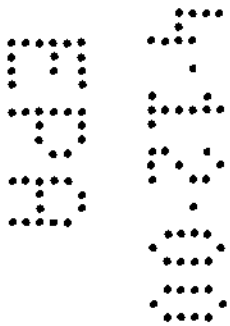
CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000



(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-Way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

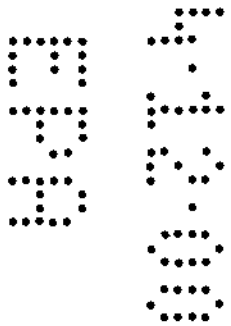
Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

READ ENTIRE LABEL BEFORE EACH USE

(Leaflet)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment for Dogs and
Puppies 7 Weeks and Older and 10 lbs and Under

READ ENTIRE LABEL BEFORE USE

For the Prevention and Treatment of Flea Infestation on Dogs.

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
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CAUTION

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DIRECTIONS FOR USE

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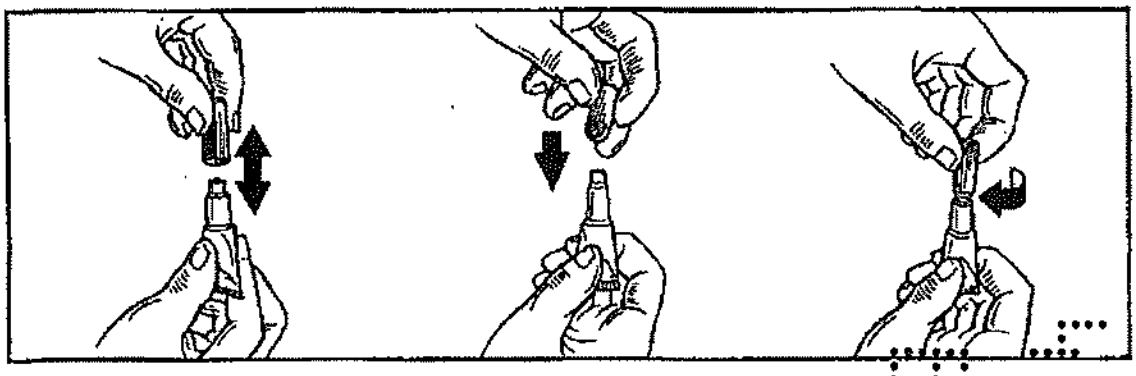
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

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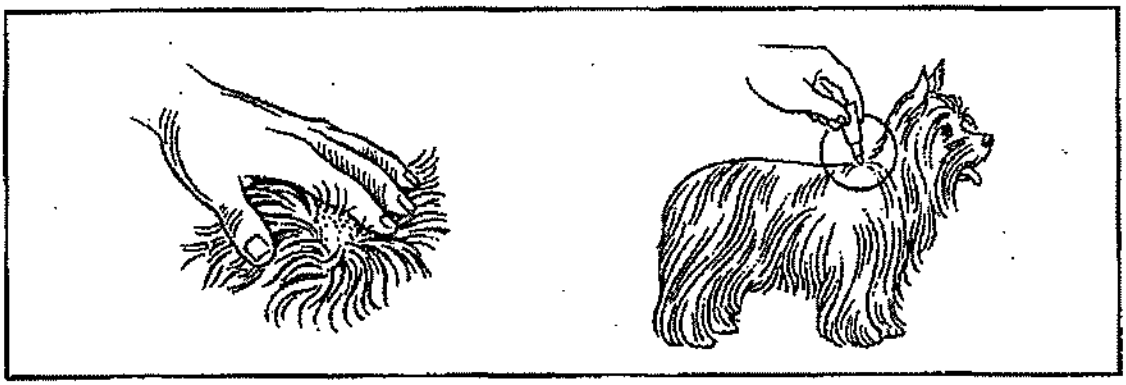

7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

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Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal:** Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal:** Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

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EPA Est. 11556-DEU-1

EPA Reg. No. 11556-XXX

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-Way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

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FIRST AID

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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Four 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

READ ENTIRE LABEL BEFORE EACH USE

(Leaflet)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment for Dogs and Puppies 7 Weeks and Older and 10 lbs and Under

READ ENTIRE LABEL BEFORE USE

For the Prevention and Treatment of Flea Infestation on Dogs.

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CAUTION

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DIRECTIONS FOR USE

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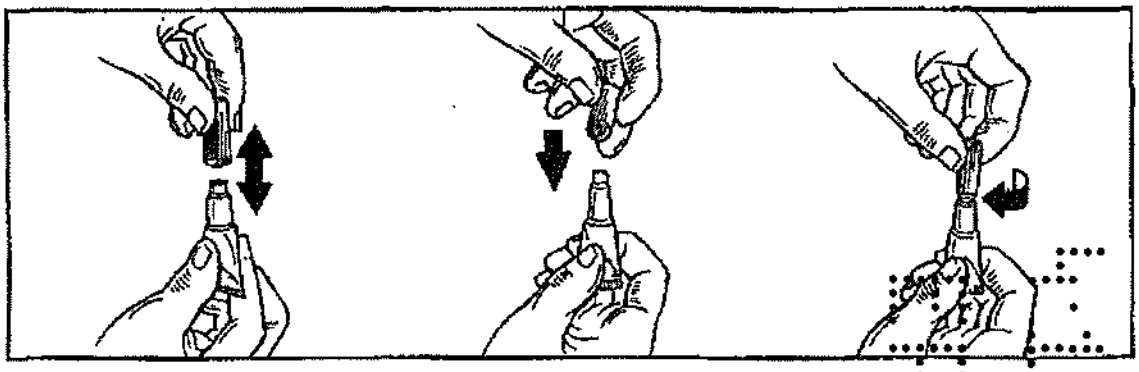
HOW TO APPLY

1. Use only on dogs. Do not use on other animals.
2. Remove one applicator tube from the package.



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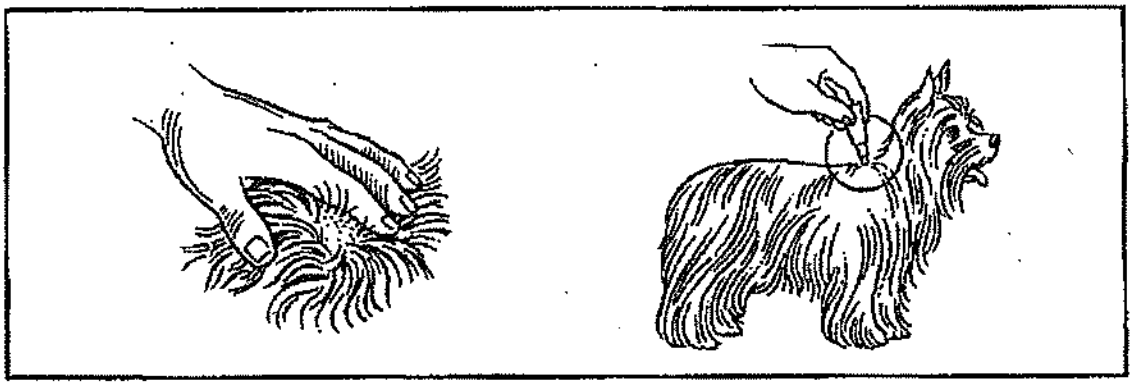

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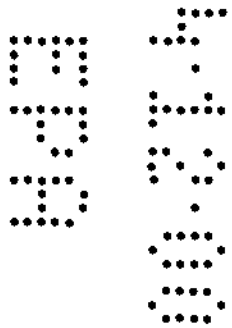
EPA Est. 11556-DEU-1

EPA Reg. No. 11556-XXX

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.



(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

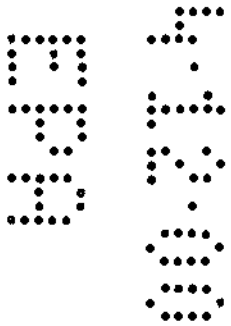
CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000



Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

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Inert Ingredients	90.44%
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KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

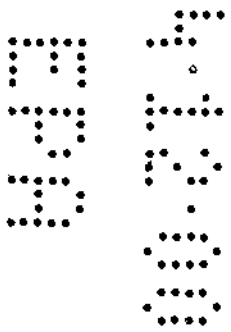
Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany



(Back Panel)

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(Leaflet)

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Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

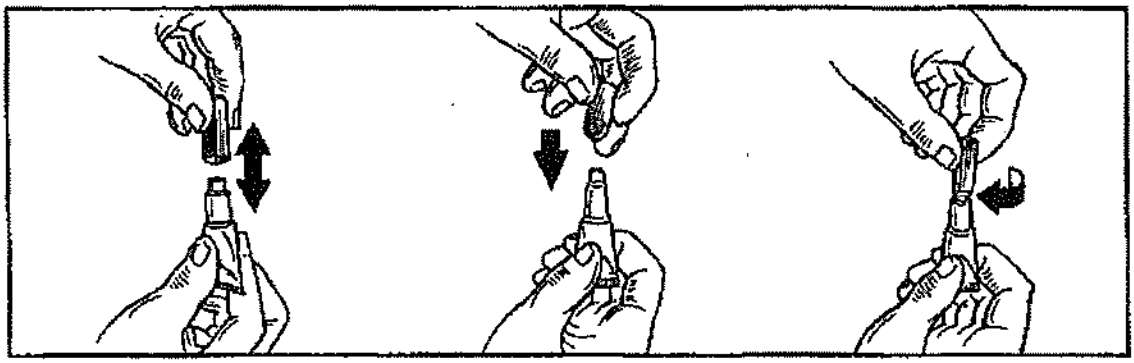
To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

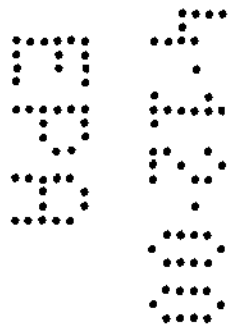
It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY

1. Use only on dogs. Do not use on other animals.
2. Remove one applicator tube from the package.

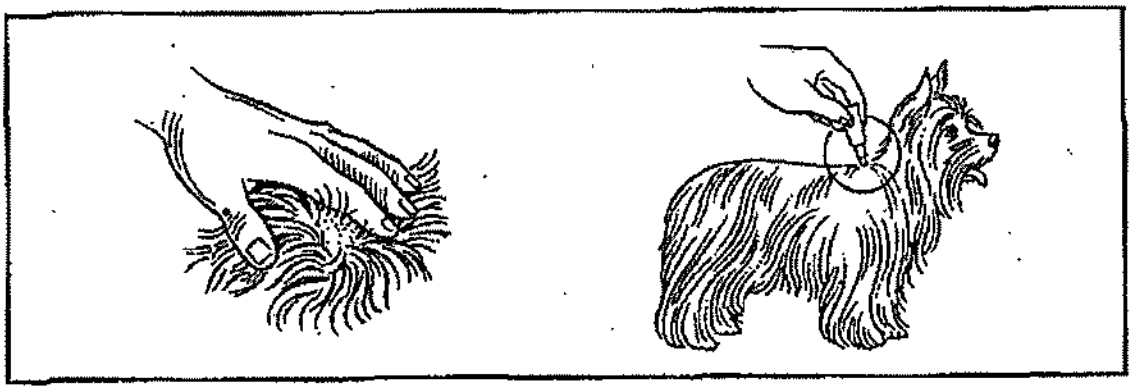


3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.



6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

   Do not get this product in your pet's eyes or mouth.



7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal:** Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal:** Do not reuse empty container. Wrap container and put in trash.

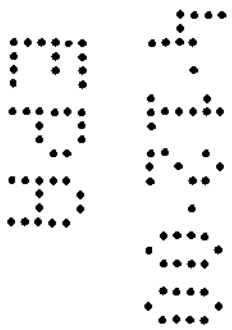
LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

EPA Est. 11556-DEU-1

EPA Reg. No. 11556-XXX

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.



(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and
Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-Way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
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KEEP OUT OF REACH OF CHILDREN

CAUTION

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PRECAUTIONARY STATEMENTS
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HAZARDS TO DOMESTIC ANIMALS

For external use only.
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FIRST AID

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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
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- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

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(Leaflet)

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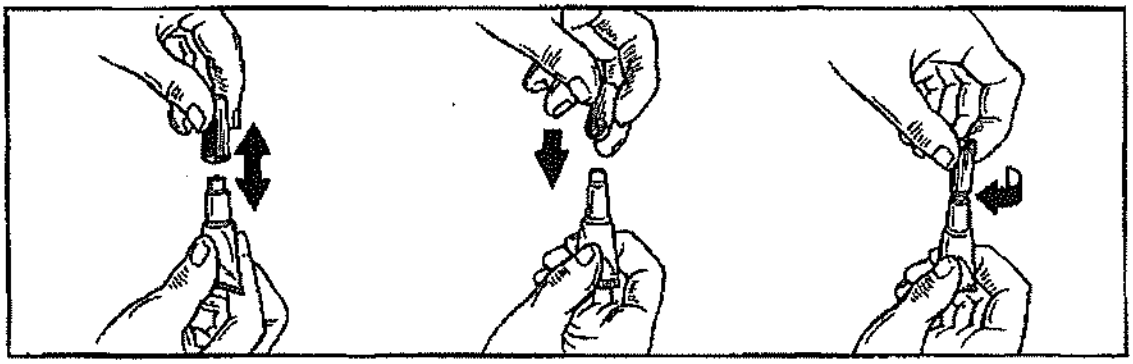

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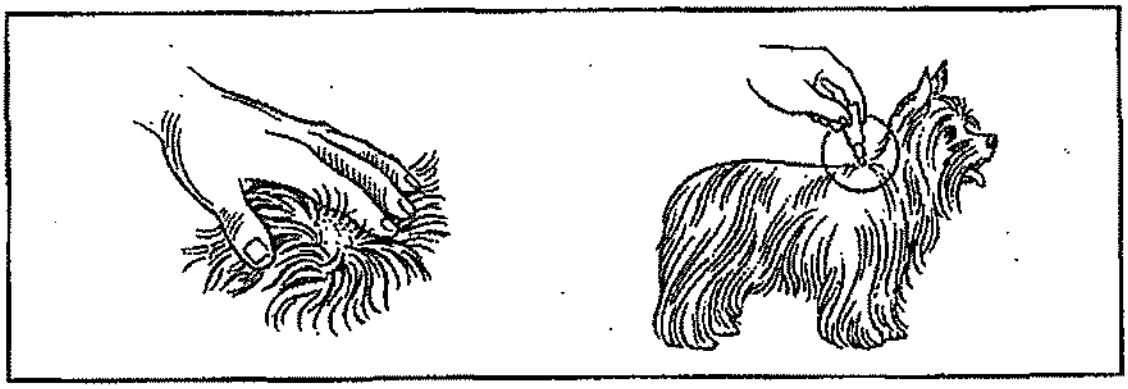

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EPA Est. 11556-DEU-1

EPA Reg. No. 11556-XXX

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
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Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
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KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

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FIRST AID

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If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
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READ ENTIRE LABEL BEFORE EACH USE

(Leaflet)

Advantage Plus® 10

Topical Solution

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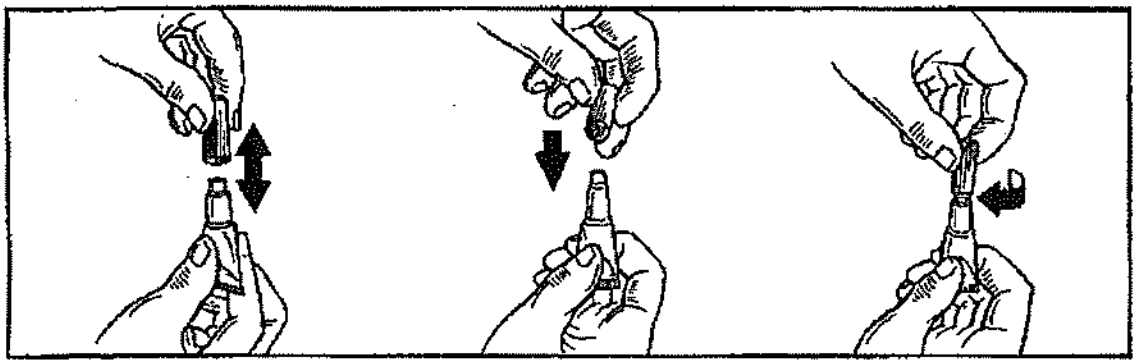

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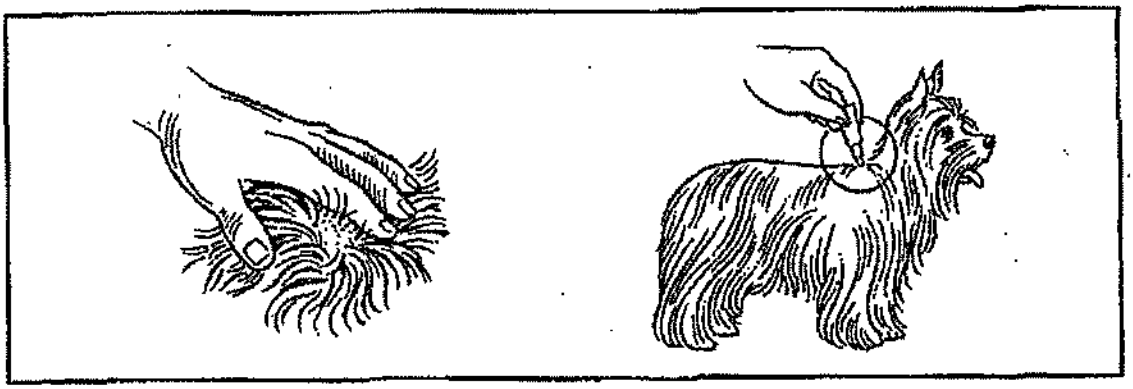

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(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

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- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
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Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
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HAZARDS TO DOMESTIC ANIMALS

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Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

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Agriculture Division
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Shawnee Mission, Kansas 66201 USA

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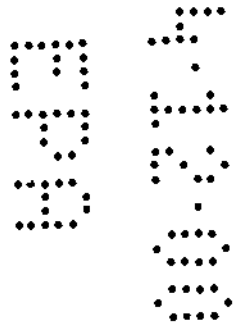

(Back Panel)

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(Leaflet)

Advantage Plus® I0

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If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

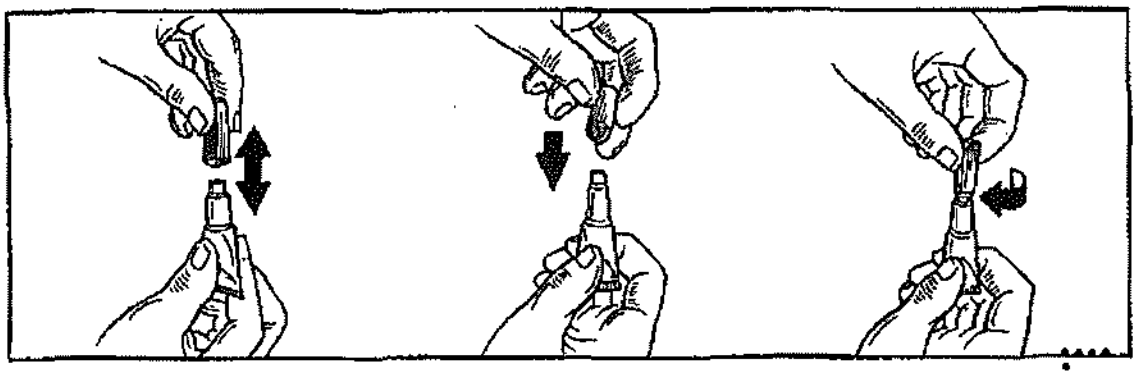
To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY

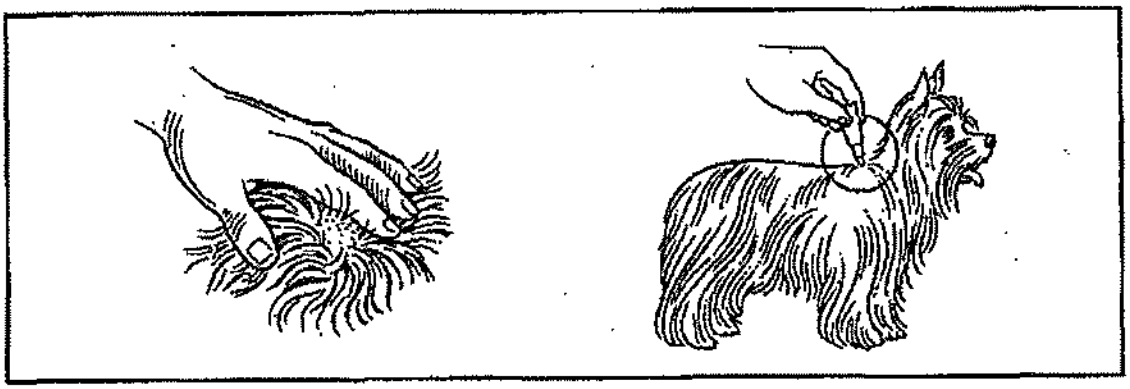
1. Use only on dogs. Do not use on other animals.
2. Remove one applicator tube from the package.



3. Hold applicator tube in an upright position. Pull cap off tube.
4. Turn the cap around and place other end of cap back on tube.
5. Twist cap to break seal, then remove cap from tube.

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

   Do not get this product in your pet's eyes or mouth.



7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage Plus® rapidly kills fleas and reduces the incidence of this condition.

Advantage Plus® kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage Plus® treated pet. Advantage Plus® provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage Plus® kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage Plus® remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place. **Pesticide Disposal:** Securely wrap original container in several layers of newspaper and discard in trash. **Container Disposal:** Do not reuse empty container. Wrap container and put in trash.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer Corporation, Agriculture Division, Animal Health warrants that this material conforms to the chemical description on the label. BAYER CORPORATION MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer Corporation is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

EPA Est. 11556-DEU-1

EPA Reg. No. 11556-XXX

Manufactured for Bayer Corporation
Agriculture Division, Animal Health
Shawnee Mission, Kansas 66201 U.S.A.

(Label on Individual Tube)

Advantage Plus®

9.10% Imidacloprid

0.46% Pyriproxyfen

0.4 mL

EPA Reg. No. 11556-XXX

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Reason To Issue: Propose Registration

Date: 04/07/00
Supersedes: None

(Front Panel)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment For Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea Infestations on Dogs

- Available Only Through Licensed Practicing Veterinarians
- Kills 98-100% of the Fleas on Dogs Within 12 Hours
- Kills Reinfesting Fleas Within 2 Hours
- One Treatment Prevents Further Flea Infestation For At Least Four Weeks
- Kills Adult Fleas, Eggs, and Larvae
- Prevents Immature Fleas from Developing into Biting, Breeding Adults
- Provides 3-Way Protection Against Fleas, Breaking Life Cycle at Egg, Larval, and Adult Stages

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

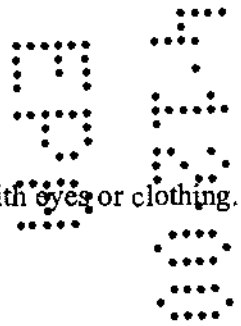
KEEP OUT OF REACH OF CHILDREN

CAUTION

See Below First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.



HAZARDS TO DOMESTIC ANIMALS

For external use only.
Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-877-258-2280.

FIRST AID

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If swallowed: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

If on skin: Wash with plenty of soap and water.

To Physician: Treat the patient symptomatically.

Six 0.4 mL Tubes

EPA Est. 11556-DEU-1
EPA Reg. No. 11556-XXX

Manufactured For

Bayer Corporation
Agriculture Division
Animal Health
Shawnee Mission, Kansas 66201 USA

Made in Germany

(Back Panel)

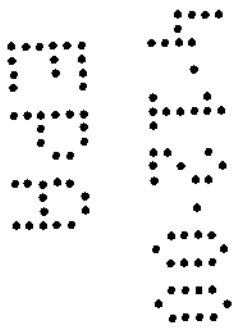
Advantage Plus® 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Flea Treatment for Dogs
and Puppies 7 Weeks and Older and 10 lbs. and Under

- Available only through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- Kills adult fleas, eggs and larvae

READ ENTIRE LABEL BEFORE EACH USE



(Leaflet)

Advantage Plus® 10

Topical Solution

Once-A-Month Topical Flea Treatment for Dogs and
Puppies 7 Weeks and Older and 10 lbs and Under

READ ENTIRE LABEL BEFORE USE

For the Prevention and Treatment of Flea Infestation on Dogs.

Active Ingredients	% By Weight
Imidacloprid; 1-[(6-Chloro-3-pyridinyl) methyl]-N-nitro-2-imidazolidinimine . .	9.10%
Pyriproxyfen; 2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine	0.46%
Inert Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN

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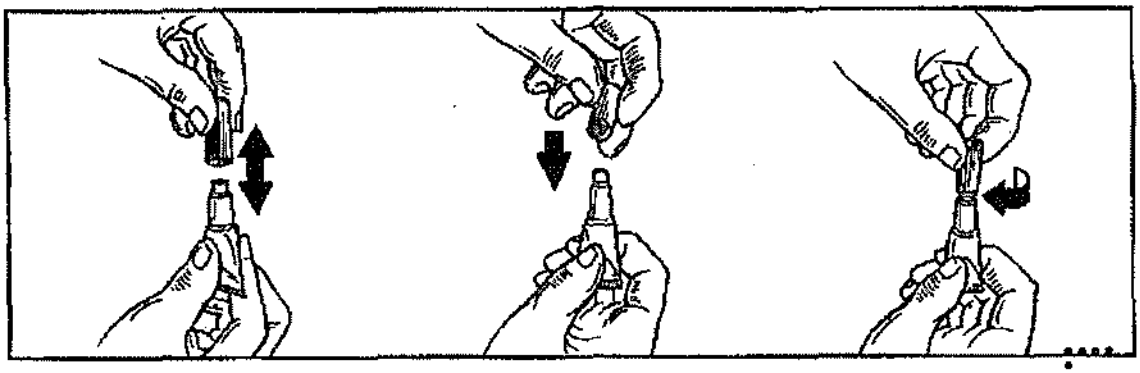

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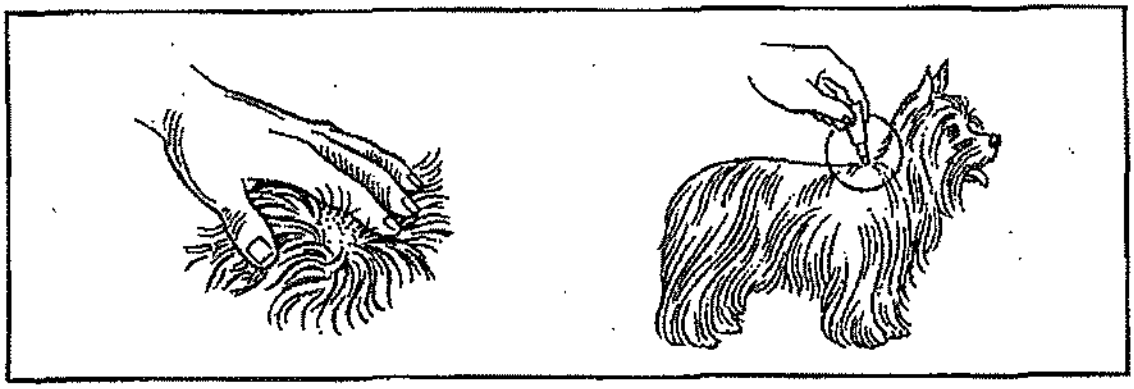

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BAYER

Lot No. 0000000

Pages 230-234 Confidential Statement of Formula may be entitled to confidential treatment